

# CARDIOLOGY I

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**Learning Objectives**

1. Distinguish between the treatment strategies for acute coronary syndrome: ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome.
2. Formulate evidence-based treatment strategies for patients with acute decompensated heart failure.
3. Devise a treatment plan for patients presenting with ventricular or life-threatening arrhythmias.
4. Differentiate between goals and treatment for hypertensive emergencies and hypertension without progressive organ damage.
5. Provide evidence-based treatment for a patient given a diagnosis of idiopathic pulmonary arterial hypertension.

**Abbreviations in This Chapter**

|       |  |
|-------|--|
| AAD   | Antiarrhythmic drug                        |
| ACE   | Angiotensin-converting enzyme              |
| ACS   | Acute coronary syndrome                    |
| ACT   | Activated clotting time                    |
| ADHF  | Acute decompensated heart failure          |
| ADR   | Adverse drug reaction                      |
| AF    | Atrial fibrillation                        |
| aPTT  | Activated partial thromboplastin time      |
| BNP   | B-type natriuretic peptide                 |
| CABG  | Coronary artery bypass grafting            |
| CAD   | Coronary artery disease                    |
| CI    | Cardiac index                              |
| CO    | Cardiac output                             |
| CPR   | Cardiopulmonary resuscitation              |
| CV    | Cardiovascular                             |
| DAPT  | Dual antiplatelet therapy                  |
| ECG   | Electrocardiogram                          |
| EF    | Ejection fraction                          |
| GI    | Gastrointestinal                           |
| GP    | Glycoprotein                               |
| GRACE | Global Registry of Acute Coronary Events   |
| HF    | Heart failure                              |
| HIT   | Heparin-induced thrombocytopenia           |
| ICD   | Implantable cardioverter-defibrillator     |
| IPAH  | Idiopathic pulmonary arterial hypertension |
| LOE   | Level of evidence                          |
| LV    | Left ventricle                             |

|          |  |
|----------|--|
| LVEF     | Left ventricular ejection fraction               |
| MAP      | Mean arterial pressure                           |
| MI       | Myocardial infarction                            |
| mPAP     | Mean pulmonary arterial pressure                 |
| NSTE-ACS | Non-ST-segment elevation acute coronary syndrome |
| NSTEMI   | Non-ST-segment elevation myocardial infarctions  |
| PAH      | Pulmonary arterial hypertension                  |
| PCI      | Percutaneous coronary intervention               |
| PCWP     | Pulmonary capillary wedge pressure               |
| PH       | Pulmonary hypertension                           |
| SCD      | Sudden cardiac death                             |
| SHD      | Structural heart disease                         |
| STEMI    | ST-segment elevation myocardial infarction       |
| SVR      | Systemic vascular resistance                     |
| SVT      | Supraventricular tachycardia                     |
| UA       | Unstable angina                                  |
| UFH      | Unfractionated heparin                           |
| VT       | Ventricular tachycardia                          |

**Self-Assessment Questions**

*Answers and explanations to these questions can be found at the end of this chapter.*

1. A 62-year-old man presents to the emergency department with the chief concern of chest pain that woke him from sleep and radiates to his jaw. An electrocardiogram (ECG) reveals ST-segment depression in leads II, III, and aVF. His blood pressure is 112/62 mm Hg, and heart rate is 60 beats/minute. Cardiac enzymes have been obtained, and the first troponin result was slightly positive. Preparations are under way to take the patient to the cardiac catheterization laboratory for evaluation. Which medication regimen is most appropriate for this patient at this time?
  - A. Aspirin 325 mg, clopidogrel 600-mg loading dose, and unfractionated heparin (UFH) infusion 80-unit/kg bolus, followed by 18 units/kg/hour and metoprolol 5 mg intravenously three times.
  - B. Aspirin 81 mg; prasugrel 60-mg loading dose; UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour; and intravenous enalaprilat.

C. Aspirin 325 mg, ticagrelor 180-mg loading dose, and UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour.

D. Aspirin 81 mg, prasugrel 60-mg loading dose, nitroglycerin infusion at a rate of 10 mcg/minute, and bivalirudin 0.75 mg/kg bolus and 1.75 mg/kg/hour infusion.

2. An 81-year-old African American man (weight 90 kg) presents to the emergency department with chest pressure (10/10 on a pain scale). His ECG reveals ST-segment depression in the inferior leads. His medical history is significant for hypertension and chronic kidney disease. Pertinent laboratory results are troponin 5.8 ng/L, serum creatinine (Scr) 3.7 mg/dL, and estimated creatinine clearance (CrCl) 20 mL/minute. The patient has been given aspirin 325 mg single dose; a nitroglycerin drip, initiated at 5 mcg/minute, will be titrated to chest pain relief and blood pressure. The patient consents for cardiac catheterization after adequate hydration. Which anticoagulation strategy is most appropriate to initiate in this patient?

A. Intravenous heparin 4000-unit intravenous bolus, followed by a 1000-unit/hour continuous infusion.

B. Enoxaparin 90 mg subcutaneously every 12 hours.

C. Fondaparinux 2.5 mg subcutaneously daily.

D. Bivalirudin 67.5-mg bolus, followed by a 157-mg/hour infusion.

3. A 56-year-old man presents to the hospital with the chief concern of chest pain that was unrelieved at home with nitroglycerin. His ECG reveals ST-segment depression and T-wave inversion. Cardiac markers show an elevated troponin I. The cardiologist has requested that the patient go to the cardiac catheterization laboratory for further evaluation. The patient has a history of coronary artery disease (CAD) and had a myocardial infarction (MI) about 6 months ago. During his previous hospitalization, the patient was thought to have developed heparin-induced thrombocytopenia (HIT) because his platelet count dropped to 40,000/mm<sup>3</sup> after his previous catheterization. Given this patient's diagnosis and history, which treatment regimen would be most appropriate during his cardiac catheterization?

A. Abciximab.

B. Bivalirudin.

C. Eptifibatide.

D. Tenecteplase.

4. A 62-year-old man presents to the emergency department after several hours of chest discomfort. His ECG reveals 1- to 2-mm ST-segment elevation in leads V<sub>1</sub>–V<sub>4</sub>, with positive troponins. He has also had increasing shortness of breath and swelling over the past 2–3 weeks. His medical history is significant for tobacco use for 40 years, chronic obstructive pulmonary disease, diabetes, and hypertension. His blood pressure is 102/76 mm Hg and heart rate is 111 beats/minute. He has rales in both lungs and 2–3+ pitting edema in his extremities. His ECG reveals an ejection fraction (EF) of 25%. After primary percutaneous coronary intervention (PCI), he is transferred to the cardiac intensive care unit. Which best describes the acute use of  $\beta$ -blocker therapy in this patient?

A. Give 12.5 mg of oral carvedilol within the first 24 hours.

B. Give 5 mg of intravenous metoprolol at bedside.

C. Give 50 mg of oral metoprolol at discharge.

D. Give no  $\beta$ -blocker at this time.

5. A 60-year-old woman with New York Heart Association (NYHA) class IV heart failure (HF) (heart failure with reduced ejection fraction [HFrEF]) is admitted for increased shortness of breath and dyspnea at rest. Her extremities appear well perfused, but she has 3+ pitting edema in her lower extremities. Her vital signs include blood pressure 125/70 mm Hg, heart rate 92 beats/minute, and oxygen saturation (Sao<sub>2</sub>) 89% on 100% facemask. After initiating an intravenous diuretic, which is the best intravenous drug to treat this patient?

A. Dobutamine.

B. Milrinone.

C. Nitroglycerin.

D. Metoprolol.

6. A 75-year-old woman has a history of NYHA class III HFrEF (left ventricular ejection fraction [LVEF] 25%) and several non-ST-segment elevation myocardial infarctions (NSTEMIs). She had an episode of sustained ventricular tachycardia (VT) during this hospitalization for pneumonia. Her corrected QT (QTc) interval was 380 milliseconds on the telemetry monitor, and her serum potassium and magnesium were 4.6 mEq/L and 2.2 mg/dL, respectively. Which intravenous agent is most appropriate for this patient?

- Procainamide.
- Metoprolol.
- Magnesium.
- Amiodarone.

7. A 53-year-old woman is admitted to the hospital after the worst headache she has ever had. Her medical history includes exertional asthma, poorly controlled hypertension, and hyperlipidemia. She is nonadherent to her medications, and she has not taken her prescribed blood pressure medications for 4 days. Vital signs include blood pressure 220/100 mm Hg and heart rate 65 beats/minute. She has a cerebrovascular accident. Which agent is most appropriate for this patient's hypertensive emergency?

- Fenoldopam 0.1 mcg/kg/minute.
- Nicardipine 5 mg/hour.
- Labetalol 0.5 mg/minute.
- Enalaprilat 0.625 mg intravenously every 6 hours.

8. A 56-year-old African American man has a long history of poorly controlled hypertension secondary to medication nonadherence and subsequent dilated cardiomyopathy (LVEF 35%). He is assessed in a community health clinic today and reports not having taken his medications for the past week. The patient is asymptomatic, and his examination is unremarkable except for blood pressure 180/120 mm Hg and heart rate 92 beats/minute. All laboratory values are within normal limits except for an SCr of 1.4 mg/dL and a urinalysis with 2+ proteinuria. Which regimen would be best to treat this patient in the clinic?

9. A 52-year-old woman experiences a witnessed cardiac arrest in a shopping mall; she is resuscitated with an automatic external defibrillator device. On electrophysiological study, she has inducible VT. Which agent is most appropriate for reducing the secondary incidence of sudden cardiac death (SCD)?

- Propafenone.
- Amiodarone.
- Implantable cardioverter-defibrillator (ICD).
- Metoprolol.

10. The Sudden Cardiac Death in Heart Failure trial evaluated the efficacy of amiodarone or an ICD versus placebo in preventing all-cause mortality in ischemic and nonischemic patients with NYHA class II and III HF. There was a 7.2% absolute risk reduction and a 23% relative risk reduction in all-cause mortality at 60 months with an ICD versus placebo. Which option best shows the number of patients needed to treat with an ICD to prevent one death versus placebo?

- 1.
- 4.
- 14.
- 43.

11. You are working on a review article about newer treatment strategies for hypertensive crises. You want to ensure that you retrieve all relevant clinical trials and related articles on your subject. Which comprehensive database is most appropriate to search to ensure that you have not missed key articles?

- International Pharmaceutical Abstracts.
- Iowa Drug Information Service.
- Clin-Alert.
- Excerpta Medica.

12. A physician on your team asks that you report an adverse drug reaction (ADR) experienced by a patient taking nesiritide. The patient had severe hypotension after the initial bolus dose of nesiritide, although his blood pressure was in the normal range before therapy initiation. The hypotension led to reduced renal perfusion, resulting in oliguric acute kidney injury and subsequent hemodialysis. The patient had no known renal insufficiency before developing this complication. Which statement best describes The Joint Commission requirements for institutional ADR reporting?

- A. A MedWatch form must be completed that explains the situation in which the ADR occurred.
- B. Institutions must create their own definition of ADR with which practitioners will be familiar.
- C. Hospital staff members must use the Naranjo algorithm to assess the severity of the ADR.
- D. Only severe or life-threatening ADRs need to be reported.

13. Your pharmacy and therapeutics committee wants you to perform a pharmacoeconomic analysis of a new drug available to treat decompensated HF. This drug works through a unique mechanism of action. Unlike other available inotropic therapies that can increase mortality, this drug appears to reduce long-term mortality. However, the cost is 10-fold greater than that of other available drugs. Which pharmacoeconomic analysis would be best to determine whether this new drug is a better formulary choice than currently available agents?

- A. Cost minimization analysis.
- B. Cost-effectiveness analysis.
- C. Cost-benefit analysis.
- D. Cost-utility analysis.

#### ***BPS Pharmacotherapy Specialty Examination Content Outline***

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

- 1. Domain 1: Patient-centered pharmacotherapy
  - a. Tasks 1:1–17, 2:1–5, 7, 3:1–5, 4:1–7, 5:1–5
  - b. Systems and patient-care problems:
    - i. Acute coronary syndrome
    - ii. Acute decompensated heart failure
    - iii. Adult cardiac arrest
    - iv. Advanced cardiac life support
    - v. Basic life support and cardiopulmonary resuscitation (CPR)
    - vi. Life-threatening arrhythmias
    - vii. Hypertensive crises (urgency and emergency)
    - viii. Pulmonary hypertension
- 2. Domain 2: Drug Information and Evidence-Based Medicine, Tasks 1:2, 3, 2:1, 5, 6, and 3:1, 2
- 3. Domain 3: System-Based Standards and Population-Based Pharmacotherapy, Tasks 1:4

## I. ACUTE CORONARY SYNDROME

### A. Definitions

1. Acute coronary syndrome (ACS) is a spectrum of conditions compatible with acute myocardial ischemia or infarction because of an abrupt reduction in coronary blood flow.
2. Atherogenic plaque rupture is the underlying pathophysiology for ACS, causing several prothrombotic substances to be released, which results in platelet activation and aggregation and eventual thrombus formation leading to partial or total occlusion of the coronary artery.
3. ACS can be divided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS)
  - a. STEMI
    - i. Defined by characteristic symptoms of myocardial ischemia in association with persistent ST-segment elevation on ECG with positive troponins
    - ii. STEMI is an indication for immediate coronary angiography to determine whether reperfusion can be performed.
  - b. NSTE-ACS
    - i. Suggested by the absence of persistent ST-segment elevation
    - ii. NSTE-ACS can be divided into unstable angina (UA) and non-STEMI (NSTEMI) according to whether cardiac biomarkers of necrosis are present. UA and NSTEMI are closely related conditions whose pathogenesis and clinical presentation are similar but vary in severity.
    - iii. Abnormalities on the ECG and elevated troponins in isolation are insufficient to make the diagnosis and must be interpreted in the appropriate clinical context (Table 1).
    - iv. Optimal inhibition of thrombosis is paramount in the management of ACS.

### B. Clinical Assessment and Initial Evaluation

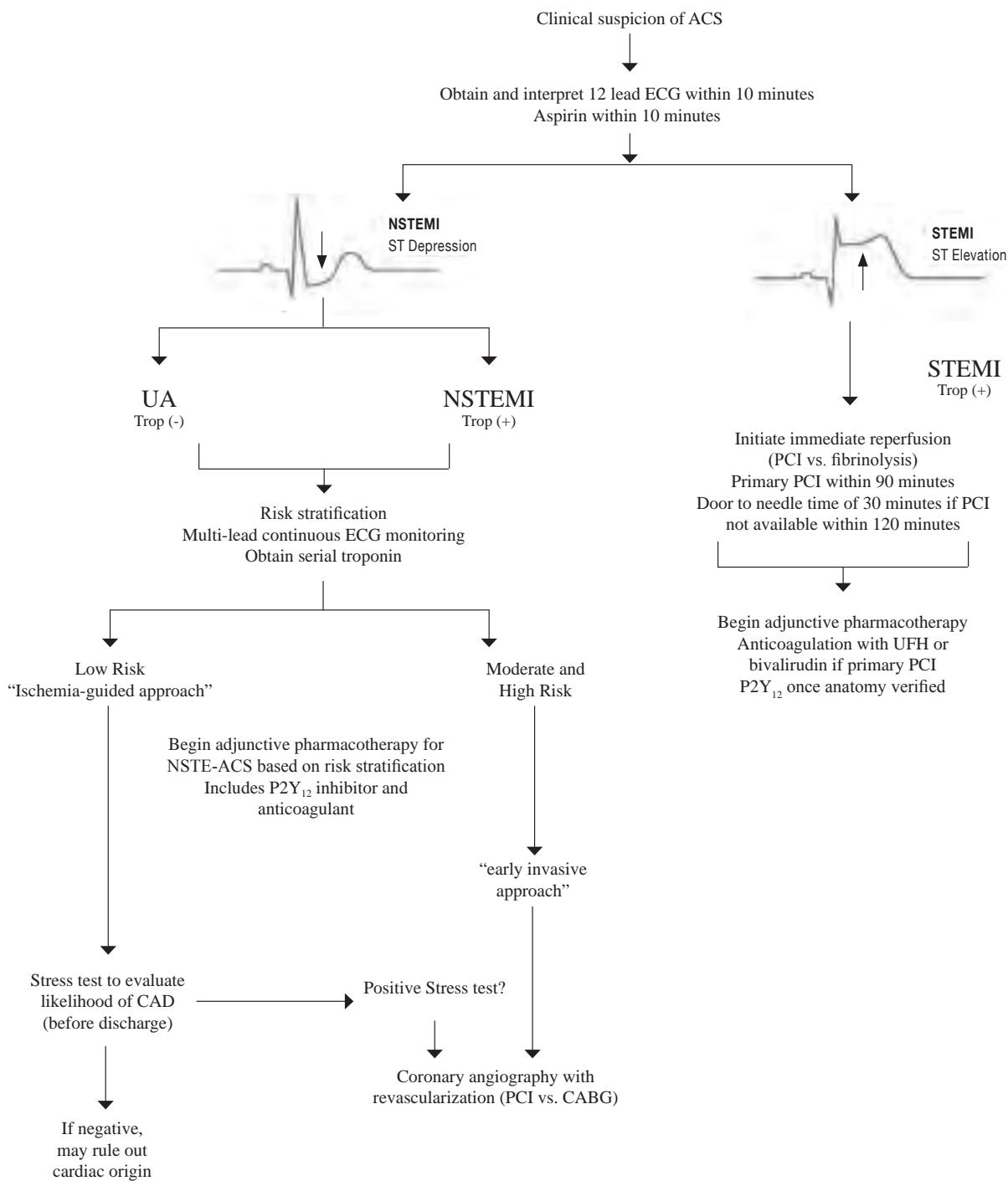
1. A 12-lead ECG should be performed and interpreted within 10 minutes of presentation.
  - a. Persistent ST-segment elevation should be treated according to the STEMI guidelines.
  - b. Serial ECGs can be performed if initial is nondiagnostic.
2. Serial cardiac troponins (I or T) should be obtained at presentation and 3–6 hours after symptom onset.
3. At initial presentation, the clinical history, angina symptoms and equivalents, physical estimation, ECG, renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events, which is useful for selecting the site of care, anti-thrombotic therapies, and invasive management. Risk calculators include the following:
  - a. Thrombolysis in myocardial infarction (TIMI) risk score (available at [www.timi.org](http://www.timi.org) [accessed December 13, 2017]) is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS.
    - i. Composed of seven 1-point indicators rated on presentation; 1 point is given for each of the following: 65 years or older, three or more risk factors for CAD, prior coronary stenosis 50% or greater, ST deviation on ECG, two or more anginal events in previous 24 hours, use of aspirin in previous 7 days, and elevated cardiac biomarkers
    - ii. Risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days; 0–2 is low risk, 3 is intermediate risk, and 4 or more is high risk
    - iii. Among patients with higher risk scores (e.g., TIMI of 3 or more), there is a greater benefit from therapies such as low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, and invasive strategies.
  - b. The Global Registry of Acute Coronary Events (GRACE) risk model ([www.outcomes-umassmed.org/grace/acs\\_risk/acs\\_risk\\_content.html](http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html) [accessed December 10, 2015]) predicts in-hospital and postdischarge mortality or MI. Patients with high GRACE risk model scores (i.e., GRACE score greater than 140) can be identified for early invasive strategies.

**Table 1.** ACS Definition

|                | <b>Subjective Findings</b>  | <b>Objective Findings</b>  | <b>Extent of Injury</b>                                    |
|----------------|---|--|--|
| NSTE-ACS<br>UA | <p>Most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion</p> <p>Pain most often starts in the retrosternal area and can radiate to either or both arms, neck, or jaw</p> <p>Pain may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope</p> <p>Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent</p> <p>Less common atypical symptoms<sup>a</sup> (without chest pain) include epigastric pain, indigestion, nausea, vomiting, diaphoresis, unexplained fatigue, and syncope</p> | <p>ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur</p> <p>No positive biomarkers for cardiac necrosis</p>     | No myocardial injury; partial occlusion of coronary artery |
| NSTEMI         |   | <p>ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur</p> <p>Positive biomarkers (troponin I or T elevation)</p> | Myocardial injury; partial occlusion of coronary artery    |
| STEMI          | Classic symptoms include worsening of pain or pressure in chest, characterized as viselike, suffocating, squeezing, aching, gripping, and excruciating, that may be accompanied by radiation  | <p>ST-segment elevation &gt; 1 mm above baseline on ECG in two or more contiguous leads</p> <p>Positive biomarkers (troponin I or T elevation)</p>       | Myocardial necrosis; total occlusion of coronary artery    |

<sup>a</sup>Up to half of all MIs are silent or unrecognized, and one-third present with symptoms other than chest discomfort.

NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI=non-ST segment elevation myocardial infarction; MI=myocardial infarction; STEMI= ST segment elevation myocardial infarction; UA = unstable angina.



**Figure 1.** ACS diagnosis and risk stratification.

CABG = coronary artery bypass grafting.

**C. Decision for Invasive Management****1. STEMI**

- a. The goal of therapy is to restore patency of the infarct-related artery and minimize infarct size. Secondary goals include prevention of complications such as arrhythmias or death as well as to control chest pain and associated symptoms.
- b. Requires urgent revascularization either interventionally or with drug therapy
- c. Primary PCI is preferred to lytic therapy. Performance measure includes goal of primary PCI within 90 minutes of first medical contact.
- d. Fibrinolytic therapy is indicated for patients with STEMI in whom PCI cannot be performed (discussed later in chapter). If PCI cannot be performed within 120 minutes, performance measure for lytic administration includes a door to needle time of 30 minutes.

**2. NSTE-ACS**

- a. The goal of therapy is to prevent total occlusion of the related artery and to control chest pain and associated symptoms. Patients with NSTE-ACS are treated on the basis of risk (TIMI, GRACE) with either an early invasive strategy (interventional approach) or an ischemia-guided strategy (a conservative management strategy using medications rather than an interventional approach).
- b. Early invasive strategy is a diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy.
  - i. Indicated in those with NSTE-ACS who have refractory angina or hemodynamic or electrical instability or those with high risk based on clinical findings
  - ii. Routine invasive therapy is generally superior to an ischemia-guided strategy (results in lower rates of recurrent UA, recurrent hospitalization, MI, and death) in patients with one or more of the following risk features: advanced age (older than 70 years), previous MI or revascularization, ST deviation, HF, depressed resting left ventricle (LV) function (i.e., LVEF less than 40%), noninvasive stress findings, high TIMI or GRACE scores, markedly elevated troponins, and diabetes.
  - iii. Not for those with serious comorbidities or contraindications to such procedures (hepatic, renal, pulmonary failure, cancer), for whom the risks for the procedure may outweigh the benefits of revascularization
  - iv. Ischemia-guided therapy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability.
    - (a) Recommended for patients with a low risk score (TIMI 0 or 1, GRACE less than 109)
    - (b) Indicated for those with acute chest pain with a low likelihood of ACS who are troponin negative (preferred for low-risk women)
    - (c) Can be chosen according to clinician and patient preference
3. All patients should receive anti-ischemic and analgesic medications early in care: morphine, oxygen, nitroglycerin, and aspirin plus  $\beta$ -blocker (Table 2).

**Table 2.** Initial Anti-ischemic and Analgesic Therapies in the Management of Acute Coronary Syndrome

| Therapy                                  | Comments  |
|--|---|
| M = Morphine or other narcotic analgesic | <p>Provides analgesia and decreased pain-induced sympathetic/adrenergic tone</p> <p>Commonly used because it can also induce vasodilation and mediate some degree of afterload reduction</p> <p>Morphine 1–5 mg IV every 5–30 min is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications<sup>a</sup></p> <p>Carries a class IIb recommendation and may not be favored more than other narcotic analgesics, given that at least two large trials have identified an association between morphine administration and risk of death<sup>b</sup></p> <p>Slows the absorption of antiplatelet therapy, reduces time to peak antiplatelet activity, and may decrease area under the curve</p>   |
| O = Oxygen                               | <p>Can help attenuate anginal pain secondary to tissue hypoxia</p> <p>Consider supplemental oxygen if <math>\text{Sao}_2 &lt; 90\%</math>, respiratory distress, or high-risk features of hypoxemia<sup>c</sup></p>   |
| N = Nitroglycerin                        | <p>Facilitates coronary vasodilation and may also be helpful in scenarios of severe cardiogenic pulmonary edema caused by venous capacitance</p> <p>NTG spray or sublingual tablet (0.3–0.4 mg) every 5 min for up to three doses to relieve acute chest pain (if pain is unrelieved after one dose, call 9-1-1); afterward, assess need for IV administration</p> <p>IV administration used in first 48 hr for treatment of persistent ischemic chest pain, HF, and HTN</p> <p>IV NTG 5–10 mcg/min; titrate to chest pain relief or max 200 mcg/min</p> <p>Use should not preclude other mortality-reducing therapies (<math>\beta</math>-blocker, ACE inhibitor)</p> <p>Contraindications: sildenafil or vardenafil (use within 24 hr) or tadalafil (use within 48 hr); <math>\text{SBP} &lt; 90</math> mm Hg or <math>\geq 30</math> mm Hg below baseline, <math>\text{HR} &lt; 50</math> beats/min, <math>\text{HR} &gt; 100</math> beats/min in absence of symptomatic HF or right ventricular infarction</p>  |
| A = Aspirin                              | <p>Inhibits platelet activation</p> <p>Mortality reducing therapy</p> <p>Chew and swallow non-enteric coated 162–325 mg <math>\times 1</math> dose<sup>c</sup></p> <p>Clopidogrel if aspirin allergy</p> <p>Performance measure</p>   |
| $\beta$ -Blocker                         | <p>Decrease myocardial ischemia, reinfarction, and frequency of dysrhythmias and increase long-term survival</p> <p>Oral <math>\beta</math>-blocker<sup>c</sup> should be initiated within 24 hr in patients who do not have signs of HF, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications to <math>\beta</math>-blockade (e.g., PR interval <math>&gt; 0.24</math> s, second- or third-degree heart block, active asthma, or reactive airway disease)</p> <p>Reasonable to continue in patients with NSTE-ACS with normal LV function<sup>a</sup></p> <p>Use metoprolol succinate, carvedilol, or bisoprolol in concomitant stabilized HFrEF<sup>c</sup>; add cautiously in decompensated HF</p> <p>Avoid agents with intrinsic sympathomimetic activity (acebutolol, pindolol, penbutolol)</p> <p>IV <math>\beta</math>-blocker<sup>d</sup> is potentially harmful in patients who have risk factors for shock (age <math>&gt; 70</math> yr, <math>\text{HR} &gt; 110</math> beats/min, <math>\text{SBP} &lt; 120</math> mm Hg, and late presentation)</p> |

<sup>a</sup>Class IIb may be considered.

<sup>b</sup>From: Montalescot G, van't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014;371:1016-27; and Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *Am Heart J* 2005;149:1043-9.

<sup>c</sup>Class I, should be performed or administered; class IIa, reasonable to be performed or administered.

<sup>d</sup>Class III, not to be administered or harmful.

ACE = angiotensin-converting enzyme; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricle; NTG = nitroglycerin; SBP = systolic blood pressure.

4. Patients with STEMI and NSTE-ACS should be treated with antiplatelet and anticoagulant therapy (Tables 3–9).

- Platelets are activated by several different mechanisms, only some of which can be inhibited by medications.
- Combination therapy with multiple antiplatelet agents plus a concomitant anticoagulant are the mainstay of acute ACS management, which targets the underlying pathophysiology of thrombus formation in ACS.
- The roles and combinations of antiplatelet therapies continue to be refined through clinical trials in varying subsets of ACS presentation (Table 3).
- In general, all patients receive aspirin and P2Y<sub>12</sub> receptor antagonists, and some patients benefit from the addition of GP IIb/IIIa inhibition in the acute management of ACS.

**Table 3.** Antiplatelet Management Strategies According to ACS Presentation

| Antiplatelet                          | NSTE-ACS<br>Ischemia Guided  | NSTE-ACS<br>Invasive   | STEMI<br>Primary PCI                   | STEMI<br>+ Fibrinolytic  |
|---------------------------------------|--|--|--|--------------------------|
| Aspirin                               | Aspirin  | Aspirin  | Aspirin                                | Aspirin                  |
| P2Y <sub>12</sub> receptor antagonist | Clopidogrel<br>Ticagrelor  | Clopidogrel<br>Prasugrel <sup>a</sup><br>Ticagrelor <sup>a</sup> | Clopidogrel<br>Prasugrel<br>Ticagrelor | Clopidogrel <sup>b</sup> |
| GP IIb/IIIa inhibitor                 | Greatest benefit when given to patients and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor <sup>c</sup> |  |  |                          |

<sup>a</sup>It may be reasonable to choose ticagrelor or prasugrel (in those who are not at high bleeding risk) over clopidogrel in patients treated with early invasive strategy for NSTE-ACS (class IIa, 2014 NSTE-ACS guideline).

<sup>b</sup>Pre-PCI after fibrinolytic therapy: 300-mg loading dose if within 24 hr of event; clopidogrel 600-mg loading dose if > 24 hr after event.

<sup>c</sup>Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with P2Y<sub>12</sub>. It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel.

GP = glycoprotein; PCI = percutaneous coronary intervention.

e. Antiplatelet recommendations

i. Aspirin

- An irreversible cyclooxygenase-1 inhibitor blocking the formation of thromboxane A<sub>2</sub> and thromboxane A<sub>2</sub>-mediated platelet activation
- Given to all patients (class I)
- Established first-line therapy in ACS; reduces the incidence of recurrent MI and death
- Loading dose is necessary for aspirin-naïve patients; avoid enteric coated initially because of delayed and reduced absorption.
  - Dosing is 162–325 mg for patients at initial presentation of ACS (Table 4).
  - Dosing is 81–325 mg for those who are undergoing PCI, depending on chronic aspirin therapy regimen.
- Aspirin is given indefinitely at a preferred dose of 81 mg after ACS with or without PCI (class I).
  - High dose (greater than 160 mg) is associated with more bleeding than lower dose (less than 160 mg).

- (2) High dose (greater than 160 mg) has not been shown to improve outcomes after ACS more effectively than lower dose (less than 160 mg).
- (f) Dual antiplatelet therapy (DAPT) with aspirin plus a P2Y<sub>12</sub> receptor inhibitor is indicated for all patients after ACS for at least 12 months (discussed later). The optimal dose of aspirin in patients treated with DAPT appears to be 75–100 mg daily.

**Table 4.** Guideline Recommendations for Aspirin Therapy in ACS with or without PCI

| Guideline Recommendation   | Class/Grade       |
|--|-------------------|
| Initiate 162–325 mg of ASA before PCI; after PCI, give ASA indefinitely <ul style="list-style-type: none"> <li>• 2013 ACCF/AHA guideline for STEMI</li> </ul>  | I                 |
| Initiate 81–325 mg of nonenteric-coated ASA before PCI in patients already taking ASA; in patients not taking ASA, give 325 before PCI; after PCI, continue ASA indefinitely <ul style="list-style-type: none"> <li>• 2014 NSTE-ACS guideline</li> <li>• 2011 ACCF/AHA/SCAI guideline for PCI</li> </ul> | I                 |
| 81 mg of ASA preferred to higher maintenance doses <ul style="list-style-type: none"> <li>• 2014 NSTE-ACS guideline</li> <li>• 2013 ACCF/AHA guideline for STEMI</li> <li>• 2011 ACCF/AHA/SCAI guideline for PCI</li> </ul>  | IIa<br>IIa<br>IIa |

Class I, should be performed or administered; Class IIa, reasonable to be performed or administered; Class IIb, may be considered; Class III, not to be administered or harmful.

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ASA = acetylsalicylic acid; SCAI = Society for Cardiovascular Angiography and Interventions.

ii. P2Y<sub>12</sub> inhibitors

- (a) Inhibit the effect of adenosine diphosphate on the platelet, a key mediator resulting in amplification of platelet activation
- (b) P2Y<sub>12</sub> inhibitor therapy is given to all patients (class I).
- (c) Choice of oral P2Y<sub>12</sub> inhibitor depends on an ischemia-guided therapy or early invasive approach and pharmacokinetic differences (Tables 5–7).
  - (1) Prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (class III).
  - (2) The efficacy of ticagrelor is decreased in patients treated with higher doses of aspirin (greater than 300 mg daily) compared with lower doses (less than 100 mg daily).
- (d) Clopidogrel and ticagrelor are preferred for a medical (i.e., ischemia-guided) strategy (Table 5).
- (e) Clopidogrel, ticagrelor, and prasugrel are options for an early invasive strategy (Table 5).
  - (1) It is reasonable to choose ticagrelor over clopidogrel for P2Y<sub>12</sub> inhibition treatment in patients with NSTE-ACS or STEMI treated with an early invasive strategy or coronary stenting (class IIa).
  - (2) It is reasonable to choose prasugrel over clopidogrel for P2Y<sub>12</sub> inhibition treatment in patients with NSTE-ACS or STEMI who undergo PCI who are not at high risk of bleeding complications and have no history of transient ischemic attack or stroke (class IIa).
- (f) No randomized data are available on the long-term safety or efficacy of “switching” patients treated for weeks or months with a P2Y<sub>12</sub> inhibitor to a different P2Y<sub>12</sub> inhibitor.

**Table 5.** Guideline Recommendations for P2Y<sub>12</sub> Inhibitor Therapy in ACS with or without PCI

| Guideline Recommendation  | Class/Grade <sup>a</sup>     |
|---|------------------------------|
| A loading dose of P2Y <sub>12</sub> receptor inhibitor should be given before PCI. Options include:<br>a. Clopidogrel <sup>b</sup> 600 mg followed by 75 mg daily<br>b. Prasugrel 60 mg followed by 10 mg daily; or<br>c. Ticagrelor 180 mg followed by 90 mg twice daily<br>• 2013 ACCF/AHA guideline for STEMI<br>• 2014 NSTE-ACS guideline | I<br>LOE B<br>LOE B<br>LOE B |
| For NSTE-ACS patients treated with an early invasive or ischemia-guided strategy:<br>a. Clopidogrel 600 mg followed by 75 mg daily<br>b. Ticagrelor 180 mg followed by 90 mg twice daily<br>• 2014 NSTE-ACS guideline   | I<br>LOE B<br>LOE B          |
| For NSTE-ACS patients treated with an early invasive or ischemia-guided strategy:<br>It is reasonable to use ticagrelor in preference to clopidogrel<br>• 2014 NSTE-ACS guideline   | IIa<br>LOE B                 |
| For NSTE-ACS patients treated with PCI who are not at risk of bleeding complications<br>• It is reasonable to choose prasugrel over clopidogrel<br>• 2014 NSTE-ACS guideline  | IIa<br>LOE B                 |
| Prasugrel should not be administered to patients with a prior history of TIA or stroke<br>• 2014 NSTE-ACS guideline<br>• 2013 ACCF/AHA guideline for STEMI  | Class III                    |

<sup>a</sup>Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

<sup>b</sup>Before PCI after fibrinolytic therapy: 300-mg loading dose if within 24 hr of event; clopidogrel 600-mg loading dose if > 24 hr after event.  
TIA = transient ischemic attack.

**Table 6.** Comparison of Oral P2Y<sub>12</sub> Receptor Inhibitors

| Parameter                   | Clopidogrel (Plavix) <sup>a</sup>   | Prasugrel (Effient) <sup>b</sup>  | Ticagrelor (Brilinta) <sup>c</sup>  |
|-----------------------------|---|---|---|
| Mechanism of action         | Thienopyridine; inhibits ADP-mediated platelet activation at the P2Y <sub>12</sub> receptor                 | Thienopyridine; inhibits ADP-mediated platelet activation at the P2Y <sub>12</sub> receptor | Inhibits ADP-mediated platelet activation at the P2Y <sub>12</sub> receptor         |
| Peak platelet inhibition    | 300 mg load ~6 hr<br>600 mg load ~2 hr  | 60-mg load ~30 min <sup>d</sup>   | 180 mg load ~30 min <sup>d</sup>  |
| % platelet inhibition       | 30%–40%   | 60%–70%   | 60%–70%   |
| Loading dose                | 300–600 mg <sup>e</sup>   | 60 mg   | 180 mg  |
| Maintenance dose            | 75 mg daily   | 10 mg daily; (5 mg if < 60 kg, BW $\geq$ 75 years) <sup>f</sup>                             | 90 mg BID <sup>g</sup>  |
| Metabolism                  | Prodrug; converted by two-step process to active metabolite involving 2C19 in addition to other CYP enzymes | Prodrug; converted by one step to active metabolite by several CYP pathways                 | Not prodrug; reversible, noncompetitive binding; 3A4 (primary), 3A5, P-gp inhibitor |
| Reversible platelet binding | No  | No  | Yes   |
| Half-life                   | 8 hr (metabolite)   | 3.7 hr (metabolite, range 2–15 hr)  | 7 hr (parent), 9 hr (active metabolite)   |
| Nonresponders               | Exposure to active drug affected by CYP2C19 genetic polymorphisms   | No known issues   | No known issues   |

**Table 6.** Comparison of Oral P2Y<sub>12</sub> Receptor Inhibitors

| Parameter   | Clopidogrel (Plavix) <sup>a</sup>  | Prasugrel (Effient) <sup>b</sup>  | Ticagrelor (Brilinta) <sup>c</sup>  |
|---|--|---|---|
| Drug-disease interactions and common nonbleeding-related adverse events | PPIs inhibit <i>CYP2C19</i> (concomitant use with esomeprazole/omeprazole is discouraged on package labeling); increased bleeding with NSAIDs, OACs, O3FAs | No clinically significant drug interactions; more bleeding with NSAIDs, OACs          | Careful with asthma, bradycardia:<br>More bleeding with NSAIDs, OACs<br>Strong 3A4 inhibitors increase ticagrelor concentrations; strong 3A4 inducers decrease ticagrelor concentrations; do not exceed 40 mg of simvastatin or lovastatin<br>Limit aspirin to < 100 mg; monitor digoxin concentrations |
| Surgery hold time <sup>d</sup>  | 5 days   | 7 days  | 5 days  |
| Bleeding risk   | Less than PRA and TIC with standard dosing   | Risk of non-CABG, spontaneous, and fatal bleeds higher than standard-dose clopidogrel | Risk of non-CABG bleeds higher than standard-dose clopidogrel   |
| Box warning   | <i>CYP2C19</i> polymorphisms   | Age-related bleeding CVA  | Aspirin dosing > 100 mg   |
| Contraindications   |  | TIA, CVA  | ICH, severe hepatic disease   |
| Supporting trials   | CREDO, CURE, PCI-CURE, CLARITY, COMMIT   | TRITON-TIMI 38, TRILOGY   | PLATO, PEGASUS  |
| FDA indication  | ACS managed medically or with PCI  | ACS with PCI  | ACS managed medically or with PCI   |

<sup>a</sup>Administer clopidogrel indefinitely if aspirin allergy. Avoid loading dose if patient is  $\geq$  75 yr in STEMI when fibrinolysis is given.

<sup>b</sup>Avoid PRA in patients with active pathological bleeding or a history of TIA or CVA and in patients  $>$  75 yr unless patient has diabetes mellitus or history of myocardial infarction.

<sup>c</sup>Avoid TIC in patients with active pathologic bleeding or a history of ICH. Avoid doses of aspirin  $>$  100 mg daily (exception: first dose of 325 mg).

<sup>d</sup>A significant antiplatelet effect has been observed at 30 min. Onset of effect is quicker, and extent of platelet inhibition is greater than with clopidogrel.

<sup>e</sup>A 600-mg loading dose results in greater, more rapid, and more reliable platelet inhibition than a 300 mg loading dose.

<sup>f</sup>Although using 5 mg in patients weighing  $<$  60 kg should be considered, this dose has not been studied in patients undergoing PCI.

<sup>g</sup>Maintenance dosing of 60 mg BID is FDA approved for reduction of thrombotic events after an initial 12 months of therapy.

<sup>h</sup>In emergency CABG, clopidogrel and ticagrelor should be held for at least 24 hr to minimize the risk of CABG-related bleeding.

ADP = adenosine diphosphate; BID = twice daily; BW = boxed warning; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; ICH = intracranial hemorrhage; NSAID = nonsteroidal anti-inflammatory drug; O3FA = omega-3 fatty acid; OAC = oral anticoagulant; P-gp = P-glycoprotein; PRA = prasugrel; TIC=ticagrelor.

### iii. Intravenous P2Y<sub>12</sub> inhibitor

- (a) Cangrelor, a direct-acting, rapidly reversible, intravenous P2Y<sub>12</sub> inhibitor, achieves a high level of platelet inhibition (greater than 90% with a 30 mcg/kg intravenous bolus followed by a 4 mcg/kg/minute infusion) within 5 minutes and reaches steady state within 15–30 minutes of administration.
- (b) Rapid onset and offset (half-life less than 5 minutes) allows quick, high degree of platelet inhibition with resolution of normal platelet function within 1 hour of ending treatment.
- (c) Primarily studied in the setting of PCI only and may be considered in those who are not candidates for oral agents

- (d) Pivotal trials comparing cangrelor with clopidogrel in ACS have not shown superiority of cangrelor; however, both the CHAMPION PHOENIX PCI and PLATFORM trials were discontinued prematurely.
- (e) Cangrelor has had better efficacy than post-PCI clopidogrel with increases in minor bleeding (not major) (CHAMPION PHOENIX).
- (f) Cangrelor treatment is associated with risk for dyspnea.
- (g) Cangrelor has not been studied in settings with preloaded clopidogrel or compared with prasugrel or ticagrelor.
- (h) Cangrelor has a potential use as a bridge therapy after discontinuation of oral P2Y<sub>12</sub> inhibitor in high-risk patients undergoing coronary artery bypass grafting (CABG) (Angiolillo 2012).
- (i) The onset of action of both clopidogrel and prasugrel is delayed when coadministered with cangrelor, suggesting that cangrelor preferentially binds to the P2Y<sub>12</sub> and prevents irreversible inhibition with prasugrel and clopidogrel's active metabolite. Therefore, clopidogrel and prasugrel should not be initiated until termination of the cangrelor infusion. No such drug interaction exists with ticagrelor.
- (j) Expense and lack of evidence demonstrating superiority to other P2Y<sub>12</sub> agents limits its use.
- (k) Cangrelor has not been included in the ACS guidelines to date because FDA approval occurred after guideline release.

- iv. Intravenous GP IIb/IIIa inhibitors
  - (a) Intravenous GP IIb/IIa receptor inhibitors can be added to aspirin with or without an oral P2Y<sub>12</sub> inhibitor for cardiovascular (CV) benefit in select high-risk patients in the acute management of ACS.
  - (b) Block the final common pathway of platelet aggregation; achieves 80% inhibition of ex vivo platelet aggregation
  - (c) GP IIb/IIIa inhibition may be beneficial in patients with high-risk features, particularly in those not adequately pretreated with P2Y<sub>12</sub> inhibition.
  - (d) Abciximab, double-bolus eptifibatide, and high-dose bolus tirofiban are class I options for invasive strategy (Table 7). Preferred options are eptifibatide and tirofiban (class IIb).
- v. GP IIb/IIIa inhibitors reduce the incidence of composite ischemic events, primarily through a decrease in documented MI, but they can increase the risk of bleeding.
- vi. Most, but not all, data were gathered in the era before routine P2Y<sub>12</sub> use.
- vii. Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (elevated biomarkers, diabetes, undergoing revascularization) and in those not receiving adequate pretreatment with clopidogrel or ticagrelor
- viii. It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel or ticagrelor.
- ix. Most studies combined GP IIb/IIIa inhibitors with UFH as the anticoagulant.
- x. Upstream administration (given before PCI) has not been shown to be superior to delayed administration (given at time of PCI).
  - (a) Upstream administration is noninferior to delayed timing for reducing ischemic events.
  - (b) Significantly higher rates of bleeding occur in those receiving upstream GP IIb/IIIa inhibitors than in those receiving delayed administration.
  - (c) Bolus-only GP IIb/IIIa inhibitor administration has been adopted in clinical practice but not into practice guidelines.

xi. Common adverse events of GP IIb/IIIa inhibitors:

- Most common adverse effect is bleeding, with rates as low as 1.4% and as high as 10.6%, depending on length of therapy and how bleeding rates were accrued in the individual studies.
- Note that the smaller-molecule agents eptifibatide and tirofiban depend on renal clearance; adjustment of the infusion is recommended to decrease risk of bleeding; monitor SCr (CrCl)
- All GP IIb/IIIa inhibitors can cause thrombocytopenia; monitor hemoglobin (Hgb), hematocrit (Hct), and platelets.
  - Rates of thrombocytopenia (platelet count less than 50,000 cells/mm<sup>3</sup>) with abciximab in clinical trials indicate 0.4%–1.4% incidence
  - When administered with UFH, rates of thrombocytopenia with either tirofiban or eptifibatide are no greater than UFH alone
- The antiplatelet effects of abciximab can be reversed by platelet transfusion, whereas those of eptifibatide and tirofiban cannot.
- Secondary to their short half-life, eptifibatide and tirofiban can be reversed within a few hours by discontinuing the infusion and are preferred options (Class IIb) in NSTE-ACS guideline .

**Table 7.** GP IIb/IIIa Inhibitor Dosing in ACS with or without PCI<sup>a</sup>

| Agent                           | Pretreated with P2Y <sub>12</sub> | Not Pretreated with P2Y <sub>12</sub>   | Renal Adjustments  |
|---------------------------------|-----------------------------------|---|--|
| Abciximab (ReoPro) <sup>b</sup> | Of uncertain benefit              | PCI: 0.25 mg/kg IVB, then 0.125 mcg/kg/min (max 10 mcg/kg) for 12 hr;<br>ACS without PCI: not recommended   | Not necessary  |
| Eptifibatide (Integrilin)       | Of uncertain benefit              | PCI: 180 mcg/kg IVB × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for 18–24 hr <sup>c</sup> ;<br>ACS without PCI: of uncertain benefit in patients adequately pretreated with a P2Y <sub>12</sub> receptor inhibitor; single bolus used as above | If CrCl < 50 mL/min/1.73 m <sup>2</sup> , reduce infusion 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL |
| Tirofiban (Aggrastat)           | Of uncertain benefit              | PCI: 25 mcg/kg IVB over 3 min; then 0.15 mcg/kg/min for 18 hr<br>ACS without PCI <sup>d</sup> : 0.4 mcg/kg/min for 30 min (LD infusion), then 0.1 mcg/kg/min for 18–72 hr   | If CrCl ≤ 60 mL/min/1.73 m <sup>2</sup> , reduce infusion 50%  |

<sup>a</sup>GP IIb/IIIa inhibitors should be used in combination with heparin (either unfractionated heparin or low-molecular-weight heparin) or used provisionally with bivalirudin and aspirin.

<sup>b</sup>Not recommended in those not undergoing PCI because of clinical trial results.

<sup>c</sup>Double bolus is recommended to support PCI in STEMI and NSTE-ACS.

<sup>d</sup>Lower dose used to treat medically managed NSTE-ACS or when there is substantial delay to PCI (i.e., 48 hr).

CrCl = creatinine clearance; IVB = intravenous bolus; LD = loading dose.

- xii. Platelet function testing
  - (a) Although platelet function can be evaluated by platelet function testing or genotyping, neither is routinely performed in the clinical setting.
  - (b) Clinical outcomes with use of platelet function testing to modify antiplatelet therapy (i.e., high-dose vs. standard-dose clopidogrel) in PCI patients with high on-treatment platelet reactivity have been negative to date. Outcomes with prospective genotype-guided anti-platelet therapy (CYP2C19) from large cohorts of PCI patients are forthcoming.
  - (c) Routine use of platelet function and genetic testing is not currently recommended (class III: no benefit).
- f. Anticoagulant recommendations
  - i. Use of anticoagulants is mainly concentrated in the procedural setting, though use may continue for a finite period after the procedure.
  - ii. Selection and use among agents may depend on ACS presentation, timing or dose of preprocedural antiplatelet medication, clot burden during procedure, and estimated risk of bleeding during procedure.
  - iii. Anticoagulants increase the risk of bleeding and will require some type of monitoring for agent-specific risks.

**Table 8.** Anticoagulant Management Strategies in ACS

| Management Strategy                           | Class I Recommendations <sup>a</sup>        |
|---|---|
| STEMI (PPCI)                                  | UFH, bivalirudin                            |
| STEMI, with fibrinolytic <sup>b</sup> therapy | UFH, enoxaparin, fondaparinux               |
| NSTE-ACS, early invasive strategy             | Enoxaparin, bivalirudin, <sup>c</sup> UFH   |
| NSTE-ACS, ischemia-guided strategy            | Enoxaparin, fondaparinux <sup>d</sup> , UFH |

<sup>a</sup>Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

<sup>b</sup>Fibrinolytics preferred when PCI cannot be performed within 120 min of first medical contact (class I). Door-to-needle time was < 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hr with IV UFH or IV/SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

<sup>c</sup>If bleeding risk is high, it is reasonable to use bivalirudin monotherapy in preference to UFH plus GP IIb/IIIa inhibitor (class IIa).

<sup>d</sup>Fondaparinux should not be used as the sole anticoagulant to support PCI. Give additional anticoagulant during revascularization if fondaparinux was initially chosen as the anticoagulant strategy. Fondaparinux is given a class I recommendation in the 2014 NSTE-ACS guidelines (for an ischemia-guided strategy) and a class III or harmful recommendation in the 2011 PCI and 2013 STEMI guidelines when PCI is indicated.

PPCI = primary percutaneous coronary intervention; UFH = unfractionated heparin.

- g. Anticoagulant agents (see Table 9 for dosing and contraindications)
  - i. UFH
    - (a) Exerts its effects as an indirect thrombin inhibitor on fibrin-bound clots
    - (b) Given as intravenous bolus with or without infusion and adjusted according to activated partial thromboplastin time (aPTT) or activated clotting time (ACT) to maintain therapeutic anticoagulation according to specific hospital protocol, usually continued for 48 hours or until PCI is performed
    - (c) Risks include bleeding, thrombocytopenia, and HIT with or without thrombosis.
    - (d) Monitoring includes aPTT or ACT, Hgb/Hct, and platelets.
    - (e) Unlike other anticoagulants, UFH is not renally cleared and can be used safely in those with renal impairment.
  - ii. Enoxaparin
    - (a) Molecular weight is one-third of UFH with balanced anti-factor Xa (anti-Xa) and anti-IIa activity.

- (b) Given as subcutaneous injection at least 2 inches on either side of the navel at a 90-degree angle into 1 inch of pinched skin (avoid injection into muscle); alternate dosing sites
- (c) Does not require routine anti-Xa monitoring; SCr to calculate CrCl for dosing; monitor Hgb, Hct, platelets
- (d) Risks include bleeding, injection site hematomas, spinal or epidural hematomas, retroperitoneal hematoma/bleeding, thrombocytopenia including HIT with or without thrombosis, mechanical prosthetic valve thrombosis (in pregnancy)

- iii. Fondaparinux
  - (a) Selective inhibitor of activated factor X
  - (b) Longest half-life of anticoagulants (17 hours)
  - (c) Given as subcutaneous injection into fatty tissue, at a 90-degree angle into a pinched skinfold; alternate dosing sites between the left and right anterolateral and posterolateral abdominal wall
  - (d) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl to assess for contraindication; monitor Hgb, Hct, platelets
  - (e) Risks include bleeding, thrombocytopenia, and spinal or epidural hematomas.
  - (f) No increased risk of HIT
- iv. Bivalirudin
  - (a) A direct thrombin inhibitor; directly inhibits thrombin in both circulating and bound clots and inhibits thrombin-mediated platelet aggregation
  - (b) Given as an intravenous bolus with or without infusion fixed rate and usually continued until the end of PCI (with or without delay after infusion in some high-risk patients)
  - (c) Does not require monitoring for adjustment; monitor SCr (adjustment required for infusion in those impaired CrCl), Hgb, Hct, platelets
  - (d) Can be given in patient with history of or suspected HIT undergoing PCI
- v. An anticoagulant should be administered to all patients with ACS in addition to antiplatelet therapy to reduce the risk of intracoronary and catheter thrombus formation (Tables 8 and 9) irrespective of initial treatment strategy.
  - (a) Enoxaparin: 30-mg intravenous bolus, then 1 mg/kg subcutaneously every 12 hours (or 1 mg/kg subcutaneously once daily for CrCl less than 30 mL/minute), continued for the duration of hospitalization or until PCI is performed
  - (b) Bivalirudin: 0.1 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients with early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor
  - (c) Fondaparinux: 2.5 mg subcutaneously daily, continued for the duration of hospitalization or until PCI is performed
  - (d) Intravenous UFH: initial bolus of 60 units/kg (maximum 4000 units) with initial infusion of 12 units/kg/hour (maximum 1000 units/hour) adjusted on the basis of aPTT to maintain therapeutic anticoagulation according to specific hospital protocol, continued for 48 hours or until PCI is performed
- vi. In an ischemia-guided strategy, UFH, enoxaparin, and fondaparinux are class I recommended options.
- vii. For an invasive strategy, UFH, enoxaparin, and bivalirudin are class I recommended options.
  - (a) Fondaparinux should not be used as the sole anticoagulant to support PCI (class III). Give additional 85 units/kg of intravenous UFH immediately before PCI revascularization to reduce risk of catheter thrombosis if fondaparinux was initially chosen as the anticoagulant strategy if no GP IIb/IIIa inhibitor is used and 60 units/kg intravenously if a GP IIb/IIIa inhibitor is used with UFH dosing according to target-activated clotting time.

- (b) Use of enoxaparin during PCI may be reasonable in patients treated with upstream subcutaneous enoxaparin with an ischemia-guided strategy.
  - (1) An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at time of PCI to patients who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous dose 8–12 hours before PCI.
  - (2) Patients who have received enoxaparin within 8 hours of the last subcutaneous dose generally have adequate anticoagulation to undergo PCI without supplemental bolus.
  - (3) Patients who undergo PCI more than 12 hours after the last subcutaneous dose are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose UFH or bivalirudin).
  - (4) In patients who have not received anticoagulant therapy, a 0.5- to 0.75-mg/kg intravenous loading dose is needed.
- (c) In those at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and GP IIb/IIIa receptor antagonist (class IIa).
  - (1) For patients who have received UFH, wait 30 minutes and then give a 0.75-mg/kg intravenous loading dose, followed by a 1.75-mg/kg/hour intravenous infusion.
  - (2) For patients already receiving bivalirudin infusion, give additional 0.5 mg/kg loading dose and increase infusion to 1.75 mg/kg/hour during PCI.
- (d) Anticoagulant therapy is generally discontinued after PCI unless there is a compelling reason to continue.

viii. In patients undergoing primary PCI, either UFH or bivalirudin is preferred.

ix. When a fibrinolytic agent is given as a reperfusion strategy, UFH, enoxaparin, and fondaparinux are recommended.

- (a) Those given fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hours with intravenous UFH or intravenous/subcutaneous enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or intravenous/subcutaneous fondaparinux during hospitalization, up to 8 days.
- (b) Bivalirudin is not recommended in this population.

**Table 9.** Antithrombotic Dosing in ACS with or without PCI

|                | <b>UFH</b>  | <b>Enoxaparin<br/>(Lovenox)</b>  | <b>Fondaparinux<br/>(Arixtra)</b> | <b>Bivalirudin<br/>(Angiomax)</b>   |
|----------------|---|--|-----------------------------------|---|
| Classification | —   | LMWH   | Factor Xa inhibitor               | Direct thrombin inhibitor   |
| NSTE-ACS       | 60 units/kg IVB (maximum 4000 units), 12 units/kg/hr IV (maximum 1000 units/hr) for 48 hr or until PCI performed; goal aPTT/anti-Xa according to hospital-specific protocol | 1 mg/kg SC every 12 hr for 24–48 hr or until PCI performed or throughout hospitalization (up to 8 days); 30 mg IVB | 2.5 mg SC daily                   | 0.1 mg/kg IVB; then 0.25 mg/kg/hr IV (only for planned invasive strategy) |

**Table 9.** Antithrombotic Dosing in ACS with or without PCI (*Cont'd*)

|  | <b>UFH</b>   | <b>Enoxaparin<br/>(Lovenox)</b>   | <b>Fondaparinux<br/>(Arixtra)</b>                               | <b>Bivalirudin<br/>(Angiomax)</b>   |
|--|--|---|---|---|
| PCI                                    | Supplemental doses to target ACT <sup>a</sup> ; if GP IIb/IIIa inhibitors, UFH 50–70 units/kg IVB; if no GP IIb/IIIa inhibitors, UFH 70–100 units/kg IVB | If last dose < 8 hr, nothing additional needed; if last dose > 8 hr, 0.3 mg/kg IVB if last dose 8–12 hr before or < 2 therapeutic doses received before PCI                                   | Fondaparinux should not be used as a sole anticoagulant for PCI | 0.75 mg/kg IVB, 1.75 mg/kg/hr IV d/c at end of PCI, or continue for up to 4 hr after procedure if needed; hold UFH 30 min before administration                                   |
| STEMI ± primary PCI                    | Supplemental doses to target ACT <sup>a</sup> ; if GP IIb/IIIa, UFH 50–70 units/kg IVB; if no GP IIb/IIIa, UFH 70–100 units/kg IVB                       | 30 mg IVB, followed immediately by 1 mg/kg SC every 12 hr; do not exceed 100 mg on first two doses; if > 75 yr, omit bolus; 0.75 mg/kg SC every 12 hr; do not exceed 75 mg on first two doses | 2.5 mg IVB; then 2.5 mg SC daily                                | 0.75 mg/kg IVB, 1.75 mg/kg/hr IV  |
| Dose adjustments and contraindications | Avoid if history of HIT  | If CrCl < 30 mL/min/1.73 m <sup>2</sup> , 1 mg/kg SC daily; avoid if history of HIT   | Contraindicated if CrCl < 30 mL/min/1.73 m <sup>2</sup>         | Adjust infusion dose in severe renal dysfunction<br>If CrCl < 30 mL/min/1.73 m <sup>2</sup> , reduce infusion to 1 mg/kg/hr; if on hemodialysis, reduce infusion to 0.25 mg/kg/hr |

<sup>a</sup>Target ACT is 250–300 s for HemoTec and 300–350 s for Hemochron without GP IIb/IIIa inhibitors and is 200–250 s in patients given concomitant GP IIb/IIIa inhibitors.

ACT = activated clotting time; aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; SC = subcutaneous(ly).

5. Fibrinolytic therapy is indicated for patients with STEMI in whom PCI cannot be performed (Table 10).
  - a. In the absence of contraindications (Table 11), fibrinolytic therapy should be given to patients with STEMI (class I when onset of ischemic symptoms is within the previous 12 hours) when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact, with an ideal door-to-needle time of less than 30 minutes.
  - b. Patients undergoing reperfusion with fibrinolysis should receive anticoagulant therapy for at least 48 hours and preferably for the duration of the index hospitalization, for up to 8 days, or until revascularization is performed.
  - c. Recommended regimens include the following:
    - i. UFH administration of a 60-unit/kg bolus (maximum 4000 units) and 12 units/kg/hour (maximum 1000 units/hour), to obtain an aPTT of 1.5–2.0 times control (about 50–70 seconds)
    - ii. Enoxaparin 30 mg intravenously (if 75 years or older, omit bolus), followed in 15 minutes by a 1 mg/kg subcutaneous injection (if 75 years or older, 0.75 mg/kg) every 12 hours for the duration of index hospitalization, for up to 8 days, or until revascularization. Maximum 100 mg for the first two doses. If 75 years or older, maximum 75 mg for the first two doses. If CrCl is less than 30 mL/minute/1.73 m<sup>2</sup>, extend dosing interval to daily administration.
    - iii. Fondaparinux administered with initial 2.5 mg intravenous dose, followed in 24 hours by 2.5 mg/day subcutaneous injections (contraindicated if CrCl is less than 30 mL/minute/1.73 m<sup>2</sup>) for the duration of the index hospitalization, for up to 8 days, or until revascularization

**Table 10.** Fibrinolytic Therapy

|                                 | <b>Dosing</b>  |
|---------------------------------|--|
| Alteplase (t-PA, Activase)      | ≤ 67 kg: 15 mg IVP over 1–2 min, then 0.75 mg/kg IV over 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over 60 min<br>> 67 kg: 15 mg IVP over 1–2 min, then 50 mg over 30 min, then 35 mg over 1 hr (maximum total dose 100 mg) |
| Reteplase (r-PA, Retavase)      | 10 units IVP; repeat 10 units IV in 30 min   |
| Tenecteplase (TNK-t-PA, TNKase) | < 60 kg: 30 mg IVP; 60–69 kg: 35 mg IVP; 70–79 kg: 40 mg IVP; 80–89 kg: 45 mg IVP; > 90 kg: 50 mg IVP (~0.5 mg/kg)   |

IVP = intravenous push; r-PA = recombinant plasminogen activator; t-PA = tissue plasminogen activator.

**Table 11.** Contraindications to Fibrinolytic Therapy

| <b>Relative Contraindications</b>  | <b>Absolute Contraindications</b>  |
|--|--|
| BP > 180/110 mm Hg on presentation or history of chronic poorly controlled HTN<br>History of ischemic stroke > 3 mo before<br>Recent major surgery (< 3 wk before)<br>Traumatic or prolonged CPR (> 10 min)<br>Recent internal bleeding (within 2–4 wk)<br>Active peptic ulcer<br>Noncompressible vascular punctures<br>Pregnancy<br>Known intracranial pathology (dementia)<br>Oral anticoagulant therapy | Any prior hemorrhagic stroke<br>Ischemic stroke within 3 mo (except in past 4½ hr)<br>Intracranial neoplasm or arteriovenous malformation<br>Active internal bleeding<br>Aortic dissection<br>Considerable facial trauma or closed-head trauma in past 3 mo<br>Intracranial or intraspinal surgery within 2 mo<br>Severe uncontrolled HTN (unresponsive to emergency therapy)<br>For streptokinase, <sup>a</sup> treatment within previous 6 mo (if considering streptokinase again) |

<sup>a</sup>Streptokinase is no longer marketed in the United States but is available in other countries.

BP = blood pressure; CPR = cardiopulmonary resuscitation.

#### D. Long-term Management After ACS

1. DAPT: 12 months
  - i. Aspirin should be continued indefinitely at a maintenance dose of 81 mg daily in all patients after ACS (class I).
  - ii. In patients who were treated with an ischemia-guided therapy, aspirin plus either clopidogrel 75 mg daily or ticagrelor 90 mg twice daily should be continued for up to 12 months.
  - iii. After PCI (bare metal stent or drug-eluting stent), aspirin plus clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be continued for at least 12 months.
2. Early discontinuation of DAPT
  - a. Early discontinuation is reasonable when the risk of morbidity exceeds the anticipated benefit (class IIa).
    - i. DAPT should be continued after ACS (with or without stent) for at least 12 months (class I).
    - ii. Shorter-duration DAPT can be considered for patients with stable ischemic heart disease who have undergone PCI with elective stent placement (class I, 6 months duration for elective PCI).
  - b. In general, shorter durations of DAPT are appropriate for those with a lower ischemic risk and a high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk with a lower bleeding risk.
    - i. No trials have compared duration of DAPT specifically in ACS.
    - ii. Prior recommendations for DAPT duration for patients treated with drug-eluting stents were based on data from first-generation stents.

- iii. Trials comparing shorter durations of DAPT have evaluated newer-generation stents in all patients undergoing PCI (including elective cases).
- iv. Compared with first-generation stents, newer-generation stents have an improved safety profile and lower risk of stent thrombosis.

3. Long-term DAPT

- a. In general, longer-duration DAPT may be reasonable for patients at higher ischemic risk with a lower bleeding risk.
- b. Trials evaluating the need for an extended duration in patients with and without ACS undergoing PCI (greater than 12 months) of DAPT therapy after PCI show a reduction in stent thrombosis and ischemia end points with increased bleeding for patients continued on DAPT beyond 12 months.
- c. The risk of stent thrombosis is greater on cessation of DAPT; however, continued DAPT beyond 1 year is unassociated with a reduction in CV or total mortality.
- d. A longer duration of P2Y<sub>12</sub> inhibitor therapy is an individualized approach according to the patient's risk of ischemia and bleeding.
  - i. It is reasonable to consider DAPT beyond 12 months if the patient is tolerating therapy and not at high risk of bleeding (class IIb).
  - ii. Durations of DAPT may be reasonable beyond 12 months if patient is at high risk and no significant history of bleeding on DAPT (class IIb).
  - iii. A DAPT score derived from the dual antiplatelet study may be useful in making decisions about whether to prolong or extend DAPT in patients treated with coronary stent implantation (Table 12).
    - (a) For those with a high DAPT score (2 or greater), prolonged DAPT reduces net (ischemic plus bleeding) events.
    - (b) For those with a low DAPT score (less than 2), the benefit-risk ratio for prolonged DAPT is not favorable (increased bleeding without a reduction in ischemic events)
    - (c) Derived from the DAPT study, which included 11,648 patients with mainly clopidogrel as P2Y<sub>12</sub> inhibitor
    - (d) Duration of DAPT more or less than 12 months should jointly be made by the clinician and the patient, balancing the risks of stent thrombosis and ischemic complications with risks of bleeding.
  - e. Ticagrelor has been shown to reduce CV end points of death, MI, and revascularization better than placebo at a reduced dose of 60 mg twice daily (after at least 12 months of 90 mg twice daily) with less bleeding than extended use of 90 mg twice daily. (Bonaca 2015)

4.  $\beta$ -Blockers

- a. Indicated for all patients unless contraindicated
- b. If not started orally within the first 24 hours, reevaluate for possible initiation before discharge.
- c. Continue for at least 3 years (when EF is greater than 40%).
- d. If moderate or severe LV failure, initiate carvedilol, bisoprolol, or metoprolol succinate with gradual titration. Continue indefinitely in patients with EF less than 40%.

5. Angiotensin-converting enzyme (ACE) inhibitors

- a. ACE inhibitors should be started and continued indefinitely for all patients with LVEF of 40% or less and in those with hypertension, diabetes mellitus, or stable chronic kidney disease unless contraindicated.
- b. ACE inhibitors may be acceptable in all other patients with cardiac or other vascular disease.
- c. Angiotensin receptor blocker is indicated if the patient has contraindications to or is intolerant of ACE inhibitors.
- d. Contraindications include hypotension, pregnancy, and bilateral renal artery stenosis.

**Table 12.** DAPT Score to Determine Favorability of Prolonged DAPT

| Factors Used to Calculate DAPT Score | Add Points for Total Score <sup>a</sup> |
|--------------------------------------|---|
| Age $\geq$ 75 yr                     | -2                                      |
| Age 65–74 yr                         | -1                                      |
| Current tobacco user                 | 1                                       |
| Diabetes mellitus                    |   |
| NSTEMI or STEMI at presentation      |   |
| Prior MI or PCI                      |   |
| Stent diameter $<$ 3 mm              |   |
| Paclitaxel-eluting stent             |   |
| CHF or LVEF $<$ 30%                  | 2                                       |
| Saphenous vein graft PCI             | 2                                       |

<sup>a</sup>A score  $\geq$  2 favors prolonged DAPT; a score  $<$  2 is of unfavorable risk-benefit.

CHF = congestive heart failure; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

From: Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;68:1082–115; and Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315:1735–49.

6. Aldosterone receptor blockers
  - a. Indicated in patients who are already receiving an ACE inhibitor and  $\beta$ -blocker after MI and who have an LVEF of 40% or less and either symptomatic HF or diabetes, unless contraindicated
  - b. Contraindications include hyperkalemia (potassium  $[K^+]$  5.0 or greater), CrCl less than 30 mL/minute/1.73 m<sup>2</sup>, and SCr greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women.
7. Lipid management: High-intensity statins are indicated in all patients after ACS without contraindication. In high-risk patients achieving a less-than-anticipated response to statins (less than a 50% reduction in LDL), or in those who are completely statin intolerant, non-statin therapy may be considered for CV benefit.
  - a. Depending on additional desired LDL percentage reduction, consideration can be given to either ezetimibe or a PCSK9 inhibitor in combination with statin therapy in very high-risk patients.
  - b. Both ezetimibe and evolocumab (given in combination with statins) have been shown to reduce CV end points.
8. Pain control
  - a. NSAIDs and select cyclooxygenase-2 inhibitors (class III) should be discontinued at time of presentation because they have been associated with increased risk of major adverse cardiac events.
  - b. Before discharge, the patient's musculoskeletal discomfort should be addressed, and a stepped-care approach should be used for selection of therapy.
  - c. Pain should be treated with acetaminophen, nonacetylated salicylates, tramadol, or narcotics at the lowest dose to control symptoms.
  - d. It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy is insufficient.
    - i. Monitor regularly for sustained hypertension, edema, worsening renal function, or gastrointestinal (GI) bleeding.
    - ii. If these occur, consider dose reduction or discontinuation.
9. Vaccination
  - a. Pneumococcal vaccination is recommended for patients 65 years and older and in high-risk patients (including smokers with asthma) with CV disease.
  - b. An annual influenza vaccination is recommended for patients with CV disease.

10. Patient education
  - a. All patients should be counseled on the duration of DAPT and the avoidance of premature discontinuation.
  - b. Patients should be educated about appropriate cholesterol management, blood pressure control, smoking cessation, and lifestyle management.
  - c. Risk factor modification should be addressed in all patients after ACS.
11. Cardiac rehabilitation: All eligible patients should be referred to a comprehensive CV rehabilitation program.

#### E. Special Populations

1. Antiplatelet recommendations in patients going on to CABG
  - a. Aspirin should be continued preoperatively to patients undergoing CABG (81–325 mg).
  - b. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days before surgery.
  - c. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding.
  - d. In patients referred for CABG, short-acting GP IIb/IIIa (eptifibatide or tirofiban) should be discontinued for at least 2 hours before surgery and abciximab for at least 12 hours to limit blood loss and transfusion.
2. Combined oral anticoagulant therapy and antiplatelet therapy in NSTE-ACS
  - a. The duration of triple antithrombotic therapy with an oral anticoagulant, low-dose aspirin, and a P2Y<sub>12</sub> inhibitor (clopidogrel preferred) should be minimized to the extent possible to limit the risk of bleeding.
  - b. Proton pump inhibitors should be prescribed to those with a history of GI bleeding (and is reasonable in those without a known history of GI bleeding) who need triple antithrombotic therapy.
  - c. Targeting a lower international normalized ratio (INR) of 2.0–2.5 may be reasonable (class IIb in NSTE-ACS guideline; class IIa in STEMI guideline) in patients needing triple therapy.
3. Older patients (i.e., 75 years or older)
  - a. Doses should be individualized by weight or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics and dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity.
  - b. Bivalirudin, rather than GP IIb/IIIa inhibitors plus UFH, is reasonable in older patients given similar efficacy but less bleeding (class IIa).
  - c. CABG may be preferred to PCI in older patients, particularly those with diabetes mellitus or complex three-vessel disease (e.g., SYNTAX score greater than 22), with or without involvement of the proximal left anterior descending artery.
4. Chronic kidney disease
  - a. CrCl should be estimated in patients with ACS, and doses of renally cleared medications should be adjusted accordingly.
  - b. Patients with chronic kidney disease undergoing coronary and LV angiography should receive adequate hydration and reduced contrast volume.
  - c. In patients with CrCl less than 60 mL/minute/1.73 m<sup>2</sup>, ticagrelor was associated with a 4% absolute risk reduction in all-cause mortality compared with clopidogrel in a prespecified analysis from PLATO without increased risk of bleeding.
  - d. No clinical trials to date have shown the utility of prasugrel in renal insufficiency.

## 5. Women

- a. Women of all ages have higher rates of in-hospital and long-term complications from ACS than men.
- b. Women derive the same benefit from aspirin, P2Y<sub>12</sub> inhibitors, anticoagulants,  $\beta$ -blockers, ACE inhibitors, and statins as men, but women may be at higher risk of adverse events.
  - i. Women incur a higher rate of bleeding complications, renal failure, and vascular complications.
  - ii. A risk score has been developed to attempt to reduce bleeding risk.
- c. Women with NSTE-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy.
- d. Women with NSTE-ACS and low-risk features should not undergo early invasive treatment because of the lack of benefit and potential for harm (class III).
- e. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given as new drugs for secondary prevention and should not be continued in previous users unless the benefits outweigh the estimated risks.
  - i. Hormone therapy increases the risk of thrombotic events, especially in the first year of therapy, and does not provide CV protection.
  - ii. Women who are more than 1 year past the initiation of hormone therapy who want to continue such therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).

**Patient Cases**

1. A 66-year-old woman (weight 70 kg) with a history of MI, hypertension, hyperlipidemia, and diabetes mellitus presents with sudden-onset diaphoresis, nausea, vomiting, and dyspnea, followed by a bandlike upper chest pain (8/10) radiating to her left arm. She had felt well until 1 month ago, when she noticed her typical angina was occurring with less exertion. Electrocardiography revealed ST-segment depression in leads II, III, and aVF and hyperdynamic T waves and positive cardiac enzymes. Blood pressure is 150/90 mm Hg, and all laboratory results are normal; SCr is 1.2 mg/dL. Home medications are aspirin 81 mg/day, simvastatin 40 mg every night, metoprolol 50 mg twice daily, and metformin 1 g twice daily. Which regimen is the best treatment strategy for this patient?
  - A. Aspirin 325 mg, ticagrelor 180 mg  $\times$  1 dose, and UFH 60-unit/kg bolus; then 12 units/kg/hour titrated to 50–70 seconds with an early invasive approach.
  - B. Aspirin 325 mg and enoxaparin 70 mg subcutaneously twice daily with an early invasive approach.
  - C. An ischemia-guided strategy with abciximab 0.25 mg/kg bolus; then 0.125 mg/kg/minute for 12 hours plus enoxaparin 80 mg subcutaneously twice daily, aspirin 325 mg/day, and clopidogrel 300 mg 1 dose; then 75 mg once daily.
  - D. An ischemia-guided strategy with aspirin 325 mg and ticagrelor 180 mg  $\times$  1 dose; plus UFH 70-unit/kg bolus; then 15 units/kg/hour.
2. A 45-year-old patient underwent an elective percutaneous transluminal coronary angioplasty and drug-eluting stent placement in her right coronary artery. Which duration best represents the minimum time DAPT should be continued?
  - A. At least 1 month.
  - B. At least 3 months.
  - C. At least 6 months.
  - D. At least 12 months.

**Patient Cases (Cont'd)**

3. A 52-year-old man (weight 100 kg) with a history of hypertension and hypertriglyceridemia presents at a major university teaching hospital with a cardiac catheterization laboratory. He has had 3 hours of crushing 10/10 substernal chest pain radiating to both arms that began while he was eating his lunch (seated), which is accompanied by nausea, diaphoresis, and shortness of breath. He has never before experienced chest pain of this character or intensity. He usually can walk several miles without difficulty and smokes 1.5 packs of cigarettes per day. Home medications are lisinopril 2.5 mg/day and aspirin 81 mg daily. Current vital signs include heart rate 68 beats/minute and blood pressure 178/94 mm Hg. Electrocardiography reveals a 3-mm ST-segment elevation in leads V<sub>2</sub>–V<sub>4</sub>, I, and aVL. Serum chemistry values are within normal limits. The first set of cardiac markers shows positive troponins, 0.8 mcg/L (normal defined as less than 0.1 mcg/L). Which regimen is best to treat this patient's STEMI?

- Reperfusion with primary PCI and stenting of occluded artery, together with abciximab 0.25 mcg/kg intravenous push, then 0.125 mcg/kg/minute, clopidogrel 300 mg 1 dose, and aspirin 325 mg 1 dose.
- Reperfusion with a reteplase 10-unit bolus twice, 30 minutes apart, plus a UFH 60-unit/kg bolus and a 12-unit/kg/hour infusion, clopidogrel, and aspirin.
- Reperfusion with tenecteplase 25-mg intravenous push 1 dose, enoxaparin 30-mg intravenous bolus plus 100 mg subcutaneously twice daily, aspirin 325 mg x 1 dose, ticagrelor 180 mg x 1 dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.
- Reperfusion with primary PCI with stenting, prasugrel 60 mg 1 dose, aspirin 325 mg 1 dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.

4. A 76-year-old male smoker (weight 61 kg) has a history of hypertension, benign prostatic hypertrophy, and lower back pain. Three weeks ago, he began to experience substernal chest pain with exertion (together with dyspnea), which radiated to both arms and was associated with nausea and diaphoresis. Episodes have increased in frequency to four or five times daily; they are relieved with rest. He has never had an ECG. Today, he awoke with 7/10 chest pain and went to the emergency department of a rural community hospital 2 hours later. He was acutely dyspneic and had ongoing pain. Home medications are aspirin 81 mg/day for 2 months, doxazosin 2 mg/day, and ibuprofen 800 mg three times daily. Vital signs include heart rate 42 beats/minute (sinus bradycardia) and blood pressure 104/48 mm Hg. Laboratory results include blood urea nitrogen (BUN) 45 mg/dL, SCr 2.5 mg/dL, and troponin 1.5 mcg/L (normal value less than 0.1 mcg/L). His ECG reveals a 3-mm ST-segment elevation. Aspirin, ticagrelor, and sublingual nitroglycerin were given in the emergency department. The nearest hospital with a catheterization laboratory facility is 2.5 hours away. Which regimen is best?

- Give alteplase 15 units intravenously plus enoxaparin 30 mg intravenous bolus.
- Use an ischemia-guided treatment strategy with UFH 4000-unit intravenous bolus, followed by 800 units intravenously per hour.
- Give tenecteplase 35 mg intravenously plus UFH 4000-unit intravenous bolus followed by 800 units intravenously per hour.
- Transfer the patient to a facility for primary PCI.

## II. ACUTE DECOMPENSATED HEART FAILURE

### A. Precipitating Factors

1. Medication related (nonadherence to medications, recent addition of negative inotropic drugs, initiation of medications that enhance salt retention, excessive alcohol or illicit drug use)
2. Disease related (nonadherence to sodium or fluid restriction, acute myocardial ischemia, uncorrected high blood pressure, pulmonary embolus, atrial fibrillation or other arrhythmias, concurrent infections, other acute CV disorders)

### B. Diagnosis

1. Must include a detailed history and physical examination
2. B-type natriuretic peptide (BNP) or NT-proBNP useful to support diagnosis and establish prognosis for acute decompensated heart failure (ADHF)
3. Hemodynamic monitoring (Table 13)
  - a. Routine use of hemodynamic monitoring with invasive intravenous lines (e.g., Swan-Ganz pulmonary artery catheters) is not recommended; however, signs and symptoms of congestion and perfusion (Table 14) or noninvasive means to determine hemodynamic values are commonly used to determine status of decompensation.
  - b. Hemodynamic monitoring with pulmonary artery catheters is helpful for evaluating patients refractory to initial therapy, for those with unknown or unclear volume status, or for those with clinical significant hypotension or worsening renal function.

**Table 13.** Hemodynamic Values in Patients with ADHF and Sepsis

| Parameter   | Normal Value      | Typical ADHF Value | Typical Sepsis Value |
|---|-------------------|--------------------|----------------------|
| Mean arterial pressure <sup>a</sup> (MAP; mm Hg)                          | 80–100            | 60–80              | 60–80                |
| Heart rate (HR; beats/min)  | 60–80             | 70–90              | 90–100               |
| Cardiac output (CO; L/min) <sup>b</sup>                                   | 4–7               | 2–4                | 5–8                  |
| Cardiac index (CI; L/min/m <sup>2</sup> ) <sup>c</sup>                    | 2.8–3.6           | 1.3–2              | 3.5–4                |
| Pulmonary capillary wedge pressure (mm Hg) <sup>d</sup>                   | 8–12 <sup>b</sup> | 18–30              | 5–8                  |
| Systemic vascular resistance (SVR; dynes/s/cm <sup>5</sup> ) <sup>e</sup> | 900–1400          | 1500–3000          | 300–800              |
| Central venous pressure (CVP; mm Hg) <sup>f</sup>                         | 2–6               | 6–15               | 2–6                  |

<sup>a</sup>MAP = diastolic blood pressure + [1/3(SBP – diastolic blood pressure)].

<sup>b</sup>CO = stroke volume × HR.

<sup>c</sup>CI = CO/body surface area.

<sup>d</sup>A range of 15–18 mm Hg is often desired or optimal in patients with HF to ensure optimal filling pressures.

<sup>e</sup>VR = [(MAP – CVP) / CO] × 80.

<sup>f</sup>BP = CO × SVR.

### C. Clinical Presentation

1. Patients with ADHF can be categorized into four subsets on the basis of fluid status and cardiac function (Figure 2).
2. “Wet or dry” is commonly used to describe volume status.
3. “Warm or cold” is used to describe cardiac function or ability to perfuse tissues.

**Table 14.** Signs and Symptoms of ADHF

| Congestion (elevated PCWP)              | Hypoperfusion (low CO)              |
|---|-------------------------------------|
| Dyspnea on exertion or at rest          | Fatigue                             |
| Orthopnea, paroxysmal nocturnal dyspnea | Altered mental status or sleepiness |
| Peripheral edema                        | Cold extremities                    |
| Rales                                   | Worsening renal function            |
| Early satiety, nausea, or vomiting      | Narrow pulse pressure               |
| Ascites                                 | Hypotension                         |
| Hepatomegaly, splenomegaly              | Hyponatremia                        |
| Jugular venous distension               |                                     |
| Hepatojugular reflux                    |                                     |

CO = cardiac output; PCWP = pulmonary capillary wedge pressure.

|                                |   | PCWP 18 mm Hg   |                |
|--------------------------------|---|---|----------------|
|                                |   | I. Warm & Dry   | II. Warm & Wet |
| CI 2.2<br>L/min/m <sup>2</sup> | PCWP normal                                       | PCWP normal   | PCWP elevated  |
|                                | CI normal<br>(compensated)                        | CI normal<br>(congested)                                      |                |
|                                | III. Cold & Dry                                   | IV. Cold & Wet  |                |
|                                | PCWP low/normal<br>CI decreased<br>(Hypoperfused) | PCWP elevated<br>CI decreased<br>(Congested and hypoperfused) |                |

**Figure 2.** Forrester hemodynamic subsets based on signs and symptoms or hemodynamic parameters in ADHF

**Table 15.** ADHF Therapy Based on Hemodynamic Subset

| Subset and description  | Treatment   |
|---|---|
| <b>Subset I: Warm and Dry</b><br>(normal parameters)<br>(PCWP 15–18 mm Hg <sup>a</sup> and CI > 2.2 L/min/m <sup>2</sup> )                  | Optimize oral medications   |
| <b>Subset II: Warm and Wet</b><br>(pulmonary or peripheral congestion)<br>(PCWP > 18 mm Hg and CI > 2.2 L/min/m <sup>2</sup> )              | IV diuretics ± IV vasodilators (venous <sup>b</sup> )<br>If symptoms persist, adjunct strategies to overcome diuretic resistance may be necessary.  |
| <b>Subset III: Cold and Dry</b><br>(hypoperfusion ± orthostasis)<br>(PCWP 15–18 mm Hg <sup>a</sup> and CI < 2.2 L/min/m <sup>2</sup> )      | If PCWP < 15 mm Hg, IVF until PCWP = 15–18 mm Hg<br>If PCWP ≥ 15 mm Hg, SBP < 90 mm Hg, IV inotrope <sup>c</sup><br>If PCWP ≥ 15 mm Hg, SBP ≥ 90 mm Hg, IV vasodilator (arterial <sup>d</sup> ) ± IV vasopressor <sup>e</sup> if needed |
| <b>Subset IV: Cold and Wet</b><br>(pulmonary/peripheral congestion + hypoperfusion)<br>(PCWP > 18 mm Hg and CI < 2.2 L/min/m <sup>2</sup> ) | IV diuretics +<br>If SBP ≥ 90 mm Hg, IV vasodilator (arterial <sup>d</sup> )<br>If SBP < 90 mm Hg, IV inotrope <sup>c</sup> ± IV vasopressor <sup>e</sup> if needed   |

<sup>a</sup>Goal PCWP is 8–12 mm Hg in a normal patient and 15–18 mm Hg in a patient with HF. If PCWP < 15 mm Hg in a patient with HF, either remove fluid restriction or cautiously administer fluids until PCWP is 15–18 mm Hg and then reassess CI.

<sup>b</sup>Venous vasodilator: Reduces PCWP.

<sup>c</sup>Compelling reason for inotrope = SBP < 90 mm Hg, symptomatic hypotension, or worsening renal function.

<sup>d</sup>Arterial vasodilator: reduce systemic vascular resistance with compensatory increase in CI.

<sup>e</sup>IV vasopressors may be required when marked hypotension precludes the use of traditional IV inotropes (e.g., septic or cardiogenic shock) but are generally avoided in ADHF

CI = cardiac index; IV = intravenous(ly); IVF = intravenous fluids; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

#### D. Chronic HF Therapy in the Setting of Acute Decompensation

1. It is recommended to continue guideline-directed medical therapies during decompensation unless hemodynamic instability or contraindications exist (e.g., hypotension, cardiogenic shock).
2. ACE inhibitors
  - a. Caution with initiation or titration during aggressive diuresis
  - b. Increases in SCr (decrease in glomerular filtration rate of 20% or more) from ACE inhibitor use are not associated with worse outcomes.
3.  $\beta$ -Blockers
  - a. Do not discontinue in patients who are stable on dose before admission (i.e., recent initiation or titration was not responsible for decompensation).
  - b. Initiation is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents.
  - c. Should be initiated at a low dose only in stable, euvolemic patients
  - d. Caution should be used when initiating in patients who have received inotropes during their hospital course.
4. Digoxin
  - a. Continue at dose to achieve serum digoxin concentration of 0.5–0.8 ng/mL.
  - b. Avoid discontinuation unless there is a compelling reason to do so, because digoxin withdrawal has been associated with worsening HF symptoms.
  - c. Caution if renal function begins to deteriorate or often fluctuates

## E. ADHF Therapy Overview (Table 15; Box 1)

1. The main drug classes used to treat ADHF include diuretics, inotropes, and vasodilators.
2. No therapy studied to date has been shown conclusively to decrease mortality.
3. Treatments are directed toward relieving symptoms, restoring perfusion, and minimizing further cardiac damage and adverse events.

**Box 1.** Overview of Acute Decompensated Heart Failure Guideline Recommendations

|   |
|---|
| <b>Diuretic therapy</b>   |
| Recommended as intravenous loop diuretics for patients with fluid overload. Change to oral route on day before discharge, if possible.  |
| When response to diuretics is minimal, the following options should be considered:  |
| <ul style="list-style-type: none"> <li>• Fluid and sodium restriction</li> <li>• Initiation of increased doses or continuous infusion of loop diuretic</li> <li>• Addition of a second diuretic with a different mechanism of action (metolazone, hydrochlorothiazide, chlorothiazide)</li> <li>• Ultrafiltration</li> </ul>  |
| <b>Inotropic therapy</b>  |
| May be considered to relieve symptoms and improve end-organ function in patients with reduced left ventricular ejection fraction and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if <ul style="list-style-type: none"> <li>• Marginal SBP (&lt; 90 mm Hg)</li> <li>• Symptomatic hypotension despite adequate filling pressure</li> <li>• No response to or intolerance of intravenous vasodilators</li> </ul> |
| May be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function  |
| <b>Vasodilator therapy</b>  |
| May be considered in addition to intravenous loop diuretics to rapidly improve symptoms in patients with acute pulmonary edema or severe hypertension (if symptomatic hypotension absent)   |
| May be considered in patients with persistent symptoms despite aggressive diuretics and oral drug therapy   |
| When adjunctive therapy is necessary in addition to loop diuretics, intravenous vasodilators should be considered over inotropic drugs  |

## F. Diuretics (Box 2): Used primarily to treat patients with pulmonary and peripheral congestion or wet (subset II or IV) HF

1. Considered first-line therapy for management of ADHF associated with fluid overload
2. No difference between bolus and continuous administration of intravenous diuretics
3. Administering high-dose intravenous diuretic (2.5 times the previous oral dose) is associated with greater fluid removal.

**Box 2. Diuretic Therapy for Acute Decompensated Heart Failure**

|  |
|--|
| <b>Loop diuretics (ascending limb of loop of Henle)</b>  |
| Most widely used and most potent, effective at low CrCl (< 30 mL/min/1.73 m <sup>2</sup> )   |
| Furosemide most commonly used; furosemide 40 mg PO = furosemide 20 mg IV = bumetanide 1 mg IV or PO = torsemide 20 mg IV or PO   |
| <b>Thiazides (distal tubule)</b>   |
| Weak diuretics when used alone, not effective at low glomerular filtration rate (CrCl < 30 mL/min/1.73 m <sup>2</sup> )  |
| Reserved for add-on therapy in patients refractory to loops  |
| <b>Diuretic resistance</b>   |
| Increase dose before increasing frequency of loop diuretic (note ceiling effect at ~160–200 mg of IV furosemide)   |
| Add a second diuretic with a different mechanism of action   |
| <ul style="list-style-type: none"> <li>• Hydrochlorothiazide 12.5–25 mg PO daily, metolazone 2.5–5 mg PO daily (30 min before loop diuretic administration)</li> <li>• Chlorothiazide 250–500 mg IV daily; consider if GI edema; generic is very expensive; reserve for NPO or refractory to other alternatives</li> </ul> |
| Continuous infusion of loop diuretic: Furosemide 0.1 mg/kg/hr IV doubled every 4–8 hr, maximum 0.4 mg/kg/hr  |
| <b>Adverse effects:</b> Electrolyte depletion (sodium, K <sup>+</sup> , magnesium), worsening renal function   |

GI = gastrointestinal; NPO = nothing by mouth; PO = oral(ly).

## G. Vasodilator Therapy (Table 16)

1. Used primarily to manage pulmonary congestion or wet (subset II or IV) HF
  - a. No data to suggest intravenous vasodilators improve outcomes
  - b. Use is limited to relief of dyspnea in those with intact blood pressure.
2. When adequate blood pressure is maintained, use in preference to inotropic therapy.
3. Venous vasodilation results in a reduction in PCWP and acute relief of shortness of breath while awaiting the onset of diuretic effects.
4. Vasodilators with arterial vasodilating properties (nitroprusside and nesiritide) can also be used as an alternative to inotropes in patients with elevated systemic vascular resistance (SVR) and low cardiac output (CO).
5. Vasodilators should be avoided in patients with symptomatic hypotension.
6. Frequent blood pressure monitoring is necessary.

**Table 16.** Vasodilator Therapy for ADHF

|                     | <b>Sodium Nitroprusside<br/>(Nipride)</b>   | <b>Nesiritide (Natrecor)</b>  | <b>IV Nitroglycerin</b>   |
|---------------------|---|---|---|
| Mechanism of action | Nitric oxide–induced stimulation of GC to convert GTP to cGMP                         | Recombinant B-type natriuretic peptide binds to natriuretic peptide receptor A to stimulate GC and production of cGMP; natriuretic mechanism unknown  | Combines with sulfhydryl groups in vascular endothelium to create S-nitrosothiol compounds that mimic nitric oxide’s stimulation of GC and production of cGMP |
| Clinical effects    | Balanced arterial and venous vasodilator  | <b>Hemodynamic effects:</b> ↓ PCWP and SVR, ↑ CI, minimal changes in HR<br><br><b>Neurohormonal effects:</b> ↓ NE, ET-1, and aldosterone<br><br>Natriuretic effects at supratherapeutic doses | Preferential venous vasodilator > arterial vasodilator, arterial vasodilation at high doses (e.g., >100 mcg/min)  |
| Indication          | Warm and wet ADHF, alternative to inotropes in cold and wet ADHF, hypertensive crises | Warm and wet ADHF, alternative to inotropes in cold and wet ADHF  | Warm and wet ADHF, ACS, or hypertensive crises  |
| Dosing              | 0.1–0.2 mcg/kg/min IV, increase by 0.2–3 mcg/kg/min every 10–20 min                   | 2 mcg/kg IVB, 0.01 mcg/kg/min IV  | 5 mcg/min IV, increase by 5 mcg/min every 5–10 minutes up to 200 mcg/min  |
| Typical dose        | 0.5–1 mcg/kg/min IV   | 0.01 mcg/kg/min IV; can omit bolus if low SBP   | 25–100 mcg/min IV, titrated to response   |
| Half-life           | < 10 min  | 18 min  | 1–3 min   |
| Elimination         | Cyanide hepatically metabolized, thiocyanate renally excreted                         | Natriuretic peptide receptor C (no renal or hepatic adjustment)   | Inactive metabolites in urine   |
| AEs                 | Hypotension or cyanide or thiocyanate toxicity  | Primarily hypotension (up to 1 hr), tachycardia (less than inotropes)   | Hypotension, reflex tachycardia, headache, tachyphylaxis  |

AE = adverse effect; cGMP = cyclic guanine monophosphate; CI = cardiac index; ET-1 = endothelin; GC = guanylate cyclase; GTP = guanosine triphosphate; IVB = intravenous bolus; NE = norepinephrine.

#### H. Inotropic Therapy (Table 17)

- Used primarily to manage hypoperfusion or cold (subset III or IV) HF
- It is important to confirm that patients in subset III have adequate filling pressures (i.e., pulmonary capillary wedge pressure [PCWP] 15–18 mm Hg) before administering inotropic therapy.
- Useful for symptom relief in patients with low systolic blood pressure (less than 90 mm Hg) or symptomatic hypotension
- Given risk of sequelae, it is reasonable to consider vasodilators before inotropes.
- Monitor continuously for arrhythmias.
- Differences in the pharmacologic effects of dobutamine and milrinone may confer advantages and disadvantages.

**Table 17.** Inotropic Therapy for ADHF

|                     | <b>Dobutamine (Dobutrex)</b>   | <b>Milrinone (Primacor)</b>   |
|---------------------|--|---|
| Mechanism of action | $\beta_1$ -Agonist: Stimulates AC to convert ATP to cAMP to $\uparrow$ CO; slight peripheral vasodilation                              | PDE inhibitor: Inhibits cAMP breakdown in heart to $\uparrow$ CO and in vascular smooth muscle to $\downarrow$ SVR            |
| Clinical effects    | Positive inotropic, chronotropic, lusitropic effects   | Positive inotropic and lusitropic effects, no direct chronotropic effects   |
| <b>Indication</b>   | <b>ADHF: Cold and wet (Forester subset IV) or cold and dry exacerbations (Forester III) (if PCWP &gt; 15 mm Hg)</b>                    |   |
| Dosing              | Start 2.5–5 mcg/kg/min IV; may titrate to maximum of 20 mcg/kg/min   | 50 mcg/kg IVB (rarely administered), then 0.1–0.2 mcg/kg/min IV; may titrate to maximum of 0.75 mcg/kg/min                    |
| Typical dose        | 5 mcg/kg/min IV  | No bolus, 0.1–0.375 mcg/kg/min IV   |
| Half-life           | 2 min  | 1 hr, prolonged to 2–3 hr if HF or CrCl < 50 mL/min/1.73 m <sup>2</sup>   |
| Elimination         | Hepatically metabolized (inactive), renally eliminated   | 90% renal   |
| AEs                 | Proarrhythmia, tachycardia, hypokalemia, myocardial ischemia, tachyphylaxis (> 72 hr); possible increased mortality with long-term use | Proarrhythmia, hypotension (avoid bolus), tachycardia, < 1% thrombocytopenia, possible increased mortality with long-term use |
| Other comments      | Consider if hypotensive  | Consider if receiving a $\beta$ -blocker  |

AC = adenylate cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CO = cardiac output; PDE = phosphodiesterase.

### I. Vasopressin Antagonists

1. Therapeutic option for managing euvolemic or hypervolemic hyponatremia in those at risk of or having active cognitive symptoms despite water restriction (i.e., serum sodium less than 125 mEq/L or less marked hyponatremia that is symptomatic and resisted correction with fluid restriction, including patients with HF and syndrome of inappropriate secretion of antidiuretic hormone)
2. Trials show effectiveness in correcting sodium with maintained therapy but no improvement in global clinical status, mortality, or reductions in rehospitalization.
  - a. Hyponatremia redevelops after therapy cessation.
  - b. Role in long-term management of HF remains unclear.
3. Tolvaptan is the only vasopressin antagonist indicated for clinically significant hyponatremia associated with HF.
  - a. Oral dosing: 15 mg daily, then titrated to 30–60 mg as needed
  - b. Pharmacology: Binds to and inhibits the V<sub>2</sub> receptor, located in the renal tubule where water reabsorption is regulated
  - c. Initiate only in hospital setting to allow monitoring of volume status and serum sodium concentrations.
  - d. Contraindicated with cytochrome P450 3A4 inhibitors (tolvaptan is a substrate of 3A4)
  - e. An overly rapid rise in serum sodium (maximum correction in any 24-hour period of chronic hyponatremia should be less than 9 mEq/L) can result in hypotension, hypovolemia, and neurological sequelae.

**Patient Case**

*Questions 5–7 pertain to the following case.*

A 72-year-old man is admitted to the hospital for HF decompensation. The patient has progressively increased dyspnea when walking (now 10 ft [3 m], previously 30 ft [6 m]) and orthopnea (now four pillows, previously two pillows), increased bilateral lower extremity swelling (3+), 13 kg of weight gain in the past 3 weeks, and dietary nonadherence. He has a history of idiopathic dilated cardiomyopathy (LVEF 25%, NYHA class III), paroxysmal atrial fibrillation (AF), and hyperlipidemia. Pertinent laboratory values are as follows: BNP 2300 pg/mL (0–50 pg/mL), K<sup>+</sup> 4.9 mEq/L, BUN 32 mg/dL, SCr 2.0 mg/dL (baseline 1.9 mg/dL), aspartate aminotransferase (AST) 40 IU/L, alanine aminotransferase 42 IU/L, INR 1.3, aPTT 42 seconds, blood pressure 108/62 mm Hg, heart rate 82 beats/minute, and SaO<sub>2</sub> 95%. Home medications include carvedilol 12.5 mg twice daily, lisinopril 40 mg/day, furosemide 80 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day.

5. Which regimen is best for treating his ADHF?
  - A. Carvedilol 25 mg twice daily.
  - B. Nesiritide 2 mcg/kg bolus, then 0.01 mcg/kg/minute.
  - C. Furosemide 120 mg intravenously twice daily.
  - D. Milrinone 0.5 mcg/kg/minute.
6. After being initiated on intravenous loop diuretics with only minimal urine output, the patient is transferred to the coronary care unit for further management of diuretic-refractory decompensated HF. His SaO<sub>2</sub> is now 87% on a 4-L nasal cannula, and an arterial blood gas is being obtained. His blood pressure is 110/75 mm Hg, and his heart rate is 75 beats/minute. The patient's SCr and K<sup>+</sup> concentrations have begun to rise; they are now 2.7 mg/dL and 5.4 mmol/L, respectively. In addition to a one-time dose of intravenous chlorothiazide, which regimen is most appropriate for this patient?
  - A. Nitroglycerin 20 mcg/minute.
  - B. Sodium nitroprusside 0.3 mg/kg/minute.
  - C. Dobutamine 5 mcg/kg/minute.
  - D. Milrinone 0.5 mcg/kg/minute.
7. The patient initially responds with 2 L of urine output overnight, and his weight decreases by 1 kg the next day. However, by day 5, his urine output has diminished again, and his SCr has risen to 4.3 mg/dL. He was drowsy and confused this morning during rounds. His extremities are cool and cyanotic, blood pressure is 89/58 mm Hg, and heart rate is 98 beats/minute. It is believed that he is no longer responding to his current regimen. A Swan-Ganz catheter is placed to determine further management. Hemodynamic values are cardiac index (CI) 1.5 L/minute/m<sup>2</sup>, SVR 2650 dynes/second/cm<sup>5</sup>, and PCWP 30 mm Hg. Which regimen is most appropriate for his current symptoms?
  - A. Milrinone 0.2 mcg/kg/minute.
  - B. Dobutamine 5 mcg/kg/minute.
  - C. Nesiritide 2 mcg/kg bolus, then 0.01 mcg/kg/minute.
  - D. Phenylephrine 20 mcg/minute.

### III. ACUTE LIFE-THREATENING ARRHYTHMIAS

#### A. Adult Cardiac Arrest (Box 3)

##### **Box 3. Select Advanced Cardiovascular Life Support Algorithms<sup>a</sup>**

|  |
|--|
| 1. Start CPR (give oxygen; attach monitor/defibrillator)                                     |
| 2. Rhythm shockable? (If yes, go to Pulseless VT/VF No. 3; if no, go to asystole/PEA No. 11) |
| <b>Algorithm for Pulseless Ventricular Tachycardia or Fibrillation</b>                       |
| 3. Defibrillation (shock 1)  |
| 4. CPR 2 min   |
| Establish IV/IO access   |
| 5. Reassess rhythm; shock if appropriate and proceed   |
| If no sign of ROSC, go to Asystole/PEA algorithm   |
| If ROSC, initiate post–cardiac arrest care   |
| 6. Defibrillation (shock 2)  |
| 7. CPR 2 min   |
| Epinephrine 1 mg IV/IO every 3–5 min   |
| Consider advanced airway, capnography  |
| 8. Reassess rhythm; shock if appropriate and proceed   |
| If no sign of ROSC, go to asystole/PEA algorithm   |
| If ROSC, initiate post–cardiac arrest care   |
| 9. Defibrillation (shock 3)  |
| 10. CPR 2 min  |
| Amiodarone <sup>b</sup> 300 mg IV/IO × 1; may repeat at 150 mg bolus × 1                     |
| Reversible causes of the event should be identified and corrected <sup>c</sup>               |
| <b>Algorithm for Asystole or PEA</b>   |
| 11. CPR 2 min  |
| IV/IO access   |
| Epinephrine 1 mg IV/IO every 3–5 min   |
| Consider advanced airway, capnography  |
| 12. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF      |
| If no sign of ROSC, proceed  |
| 13. CPR 2 min  |
| Treat reversible causes <sup>c</sup>   |
| 14. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF      |
| If no sign of ROSC, continue steps 11–14   |
| If ROSC, initiate post–cardiac arrest care   |

<sup>a</sup>If no IV/IO access, endotracheal administration of epinephrine, lidocaine, and atropine is allowed at 2–2.5 times the recommended IV/IO dose. Dilute this dose with 5–10 mL of sterile water or normal saline.

<sup>b</sup>If amiodarone is unavailable, lidocaine may be considered. Lidocaine 1–1.5 mg/kg IV, repeat 0.5–0.75 mg/kg IV/IO every 5–10 min (maximum 3 mg/kg). Lidocaine has not been shown to improve ROSC and hospital admission compared with amiodarone.

<sup>c</sup>Hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia or hyperkalemia, hypothermia, tension pneumothorax, tamponade (cardiac), toxins, thrombosis (pulmonary), thrombosis (coronary).

CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

**B. Symptomatic Bradycardia**

1. If unstable, atropine 0.5 mg every 3–5 minutes (maximum dose 3 mg). (Note: Unstable = hypotension, acutely altered mental status, signs of shock, ischemic chest discomfort, acute HF)
2. If atropine fails, transcutaneous pacing, dopamine 2–10 mcg/kg/minute, or epinephrine 2–10 mcg/minute

**C. Symptomatic Tachycardia**

1. If unstable, synchronized cardioversion
2. If stable, determine whether QRS complex is narrow or wide.
  - a. Narrow-complex tachycardia (QRS less than 120 milliseconds); usually atrial arrhythmias
    - i. Regular ventricular rhythm: Supraventricular tachycardia (SVT) or sinus tachycardia likely
      - a. Vagal maneuvers or adenosine 6 mg intravenous push, followed by a 20 mL saline flush, then a 12 mg intravenous push (may repeat once)
        - 1) Rapid push followed by elevation of arm to increase circulation
        - 2) Larger doses may be needed in patients taking theophylline or caffeine.
        - 3) Initial dose should be reduced to 3 mg in patients taking dipyridamole or carbamazepine and in patients after heart transplantation, and when the drug is being given by central access.
        - 4) Use adenosine cautiously in severe CAD.
        - 5) Adenosine should not be given to patients with asthma.
        - 6) Do not give adenosine for unstable or for irregular or polymorphic wide complex tachycardias, because it can cause degeneration to ventricular fibrillation (VF).
      - b. If vagal maneuvers or adenosine fails to convert paroxysmal SVT, calcium channel blockers (CCBs) or  $\beta$ -blockers can be used. If Wolff-Parkinson-White syndrome, avoid verapamil, diltiazem, and digoxin
    - ii. Irregular (narrow complex) ventricular rhythm: AF (or possibly atrial flutter)
      - a. General management should focus on control of the rapid ventricular rate.
        - 1) Usually non-dihydropyridine CCBs (diltiazem, verapamil) or  $\beta$ -blockers; digoxin sometimes useful
        - 2) Rate is acceptable if it is less than 110 beats/minute at rest in asymptomatic persistent AF.
      - b. If patient is hemodynamically unstable, synchronized cardioversion is recommended.
      - c. Patients with AF for more than 48 hours are at high risk of cardioembolic events and should not be immediately cardioverted if stable.
      - d. Transesophageal echocardiography before cardioversion is an alternative strategy to ensure the absence of left atrial clot.
      - e. Risk of thromboembolic event surrounding cardioversion (both pharmacologic and electrical) is greatest within the first 10 days.
      - f. Cardioversion
        - 1) If AF for up to 7 days, either elective direct current conversion or chemical cardioversion
          - A) Flecainide, dofetilide, propafenone, ibutilide, or amiodarone (proven efficacy)
          - B) Digoxin and sotalol are not recommended and may be harmful.
          - C) Disopyramide, quinidine, and procainamide are less effective or incompletely studied.
        - 2) If AF greater than 7 days, administer either elective direct current conversion or chemical cardioversion with dofetilide, amiodarone, or ibutilide (proven efficacy).

b. Wide complex tachycardia (QRS greater than 120 milliseconds): Usually ventricular arrhythmias

- Ventricular tachycardia (VT) or unknown mechanism
  - Consider adenosine only if regular and monomorphic.
  - Intravenous procainamide, amiodarone (or sotalol); lidocaine second line
  - Avoid procainamide and sotalol if prolonged QTc.
- Definite SVT with aberrancy: Probably transiently slowed or converted by adenosine
- Polymorphic (irregular) VT
  - Induced primarily when the QTc interval is greater than 500 milliseconds (torsades de pointes)
  - If unstable, polymorphic (irregular) VT requires immediate defibrillation with the same strategy as VF.
  - If stable, intravenous magnesium ( $Mg^{2+}$ ) 1–2 g intravenous bolus (maximum 16 g every 24 hours) may be given; however, this is supported only by observational studies in the setting of wide QRS.
  - Withdrawal of QT-prolonging medications, correction of low  $Mg^{2+}$  or  $K^+$  levels
    - Class I and III antiarrhythmic drugs
    - Assess for drug interactions by cytochrome P450 3A4 (e.g., azole antifungals, erythromycin).
    - Assess for other QTc-prolonging drugs such as haloperidol, ziprasidone, droperidol, promethazine, macrolide and quinolone antibiotics, tricyclic antidepressants, or drugs contraindicated with dofetilide such as sulfamethoxazole/trimethoprim or thiazides.

D. Antiarrhythmic Overview (Tables 18 and 19)

**Table 18.** Vaughn-Williams Antiarrhythmic Drug Classes

| Class/Ion Affected                               | Agents   | Physiological Effect                            | Result on Electrophysiological Parameters | Clinical Utility   |
|--|--|---|---|--|
| <b>Class I/Na<sup>+</sup> channel blockers</b>   |  |   |   |  |
| Ia (intermediate)                                | Disopyramide<br>quinidine,<br>procainamide   | ↓ Conduction velocity;<br>↑ refractory period   | ↑ QRS complex and<br>↑ QT interval        | Atrial and ventricular arrhythmias                       |
| Ib (fast)  | Lidocaine, mexiletine,<br>phenytoin  | ↓ Conduction velocity;<br>↓↑ refractory period  | ↓ QT interval                             | Ventricular arrhythmias                                  |
| Ic (slow)  | Flecainide, propafenone  | ↓↓ Conduction velocity;<br>Ø refractory period  | ↑ QRS complex                             | Supraventricular arrhythmias and ventricular arrhythmias |
| <b>Class II</b><br>β-blockers                    | Metoprolol, esmolol,<br>atenolol   | ↓ Conduction velocity;<br>↑ refractory period   | ↓ HR and ↑ PR interval                    | Atrial and ventricular arrhythmias                       |
| <b>Class III K<sup>+</sup> channel blockers</b>  | Amiodarone, <sup>a</sup><br>dronedarone, <sup>a</sup> sotalol, <sup>b</sup><br>dofetilide, ibutilide | Ø Conduction velocity;<br>↑↑↑ refractory period | ↑ QT interval                             | Atrial and ventricular arrhythmias                       |
| <b>Class IV Ca<sup>2+</sup> channel blockers</b> | Diltiazem, verapamil   | ↓ Conduction velocity;<br>↑ refractory period   | ↓ HR and ↑ PR interval                    | Atrial and ventricular arrhythmias                       |

<sup>a</sup>Amiodarone and dronedarone have Ib, II, and IV class activity in addition to class III actions.

<sup>b</sup>Sotalol has 50%/50% β-blocking properties/K<sup>+</sup>-blocking properties.

$Ca^{2+}$  = calcium;  $Na^+$  = sodium. ↑= increases; ↓=decreases; Ø= no effect

**Table 19.** Antiarrhythmic Drug Properties and Dosing (class I and III agents only)

| Drug   | AEs, Contraindications, Pharmacokinetics, and Drug Interactions   | Dosing by Indication   |
|--|---|--|
| <b>Class Ia: Na<sup>+</sup> channel blockers</b> |   |  |
| Quinidine<br>(Quinidex,<br>Quinaglute)           | AEs: Nausea, vomiting, and diarrhea (30%), “cinchonism” (CNS and GI symptoms, tinnitus), strong vagolytic and anticholinergic properties, TdP (first 72 hr), hypotension, GI upset<br><br>PK: Half-life 5–9 hr<br><br>Potent inhibitor of CYP2D6; substrate and inhibitor of CYP3A4<br><br>DIs: Warfarin, digoxin | AF conversion:<br>Avoid use because of GI AEs<br>AF and VT maintenance:<br>Sulfate: 200–400 mg PO every 6 hr<br>Gluconate (CR): 324 mg PO every 8–12 hr<br>Decrease dose 25% if CrCl < 10 mL/min/1.73 m <sup>2</sup>   |
| Procainamide<br>(Pronestyl)                      | AEs: hypotension (IV use, 5%), TdP<br><br>CI: LVEF < 40%<br><br>PK: Active metabolite NAPA (class III effects) may accumulate in renal dysfunction  | AF conversion: 1 g IV for 30 min; then 2 mg/min (1-hr efficacy 51%)<br><br>AF maintenance: No oral agent available<br>VT conversion: 20 mg/min IV until 17 mg/kg, arrhythmia ceases, hypotension, or QRS widens > 50%<br><br>VT maintenance: 1–4 mg/min<br><br>Reduce dose in renal and liver dysfunction  |
| Disopyramide<br>(Norpace,<br>Norpace CR)         | AEs: Anticholinergic effects, TdP, ADHF (potent negative inotropic effect)<br><br>CIs: Cardiogenic shock, congenital long QT syndrome, second- or third-degree AVB, glaucoma<br><br>PK: Half-life 4–8 hr<br><br>Substrate of CYP2D6<br><br>DI: May enhance the effect of β-blockers                               | AF conversion: IR 200 mg (if < 50 kg) or 300 mg (if > 50 kg) PO every 6 hr<br><br>AF maintenance: 400–800 mg/day in divided doses (recommended adult dose 600 mg/day given as IR 150 mg PO every 6 hr or as CR 300 mg PO every 12 hr)<br><br>If < 50 kg, moderate renal dysfunction (CrCl > 40 mL/min/1.73 m <sup>2</sup> ) or hepatic dysfunction, maximum 400 mg/day<br><br>If severe renal dysfunction (IR only; avoid CR) CrCl 30–40 mL/min/1.73 m <sup>2</sup> , 100 mg every 8 hr<br><br>CrCl 15–30 mL/min/1.73 m <sup>2</sup> , 100 mg every 12 hr<br><br>CrCl < 15 mL/min/1.73 m <sup>2</sup> , 100 mg every 24 hr<br><br>Ventricular tachycardias: Use has fallen out of favor because of the availability of newer agents with less toxicity |
| <b>Class Ib: Na<sup>+</sup> channel blockers</b> |   |  |
| Lidocaine<br>(Xylocaine)                         | AEs: CNS (perioral numbness, seizures, confusion, blurry vision, tinnitus)<br><br>CI: Third-degree AV heart block<br><br>PK: Reduce dose in those with HF, liver disease, low body weight, and renal dysfunction and in older adults<br><br>DI: Amiodarone (increased lidocaine levels)                           | Pulseless VT/VF conversion or VT with a pulse:<br>1–1.5 mg/kg IVP; repeat 0.5–0.75 mg/kg every 3–5 min (maximum 3 mg/kg)<br>(If LVEF < 40%, 0.5–0.75 mg/kg IVP)<br>(Amiodarone DOC in pulseless VT/VF; lidocaine acceptable if amiodarone not available)<br><br>VT maintenance: 1–4 mg/min<br><br>Reduce maintenance infusion in liver disease   |
| Mexiletine<br>(Mexitil)                          | AEs: CNS (tremor, dizziness, ataxia, nystagmus)<br><br>CI: Third-degree AV heart block<br><br>PK: Half-life 12–20 hr<br><br>Substrate CYP2D6, CYP1A2<br><br>Inhibitor CYP1A2  | VT maintenance: 200–300 mg PO every 8 hr; maximum 1200 mg/day<br><br>Reduce dose by 25%–25% in hepatic impairment  |

**Table 19.** Antiarrhythmic Drug Properties and Dosing (class I and III agents only) (Cont'd)

| Drug   | AEs, Contraindications, Pharmacokinetics, and Drug Interactions   | Dosing by Indication  |
|--|---|---|
| <b>Class Ic: Na<sup>+</sup> channel blockers (Note: Avoid in patients with HF or after MI; increased risk of sudden death)</b> |   |   |
| Propafenone <sup>a</sup><br>(Rythmol,<br>Rythmol SR)   | AEs: Metallic taste, dizziness, ADHF, bronchospasm, bradycardia, heart block (negative inotropy and β-blocking properties)<br>CIs: HF (NYHA III–IV), liver disease, valvular disease (TdP), CAD, MI<br>PK: Half-life 10–25 hr<br>Substrate CYP2D6, CYP1A2, CYP3A4<br>Inhibitor CYP1A2, CYP2D6<br>DIs: Digoxin ↑ by 70%; warfarin ↑ by 50% as well as drugs that inhibit CYP 2D6, 1A2, 3A4 (increased propafenone)   | AF conversion:<br>600 mg PO × 1 (efficacy 45% at 3 hr)<br>450 mg PO × 1 (weight < 70 kg)<br>AF maintenance:<br>HCl: 150–300 mg PO every 8–12 hr<br>HCl (SR): 225–425 mg PO every 12 hr<br>Reduce dose 70%–80% in hepatic impairment   |
| Flecainide <sup>a</sup><br>(Tambocor)  | AEs: Dizziness, tremor, ADHF (negative inotropy), vagolytic, anticholinergic, hypotension<br>CIs: HF, CAD, valvular disease, LVH (TdP)<br>PK: Half-life 10–20 hr<br>Substrate CYP2D6, CYP1A2<br>Inhibitor CYP2D6<br>DI: Digoxin ↑ by 25%  | AF conversion: 300 mg PO × 1 (efficacy 50% at 3 hr)<br>AF maintenance: 50–150 mg PO BID<br>Reduce dose by 50% when CrCl < 50 mL/min/1.73 m <sup>2</sup>   |
| <b>Class III: K<sup>+</sup> channel blockers</b>   |   |   |
| Amiodarone<br>(Cordarone)  | AEs: Pulmonary fibrosis 3%–17%, hyperthyroidism 3%, hypothyroidism 30%, neurological toxicity 20%–40%, GI upset, photosensitivity, corneal deposits, hepatitis, blue-gray skin 15%, TdP < 1%, heart block 14%, hypotension (IV), phlebitis (IV; Ca <sup>2+</sup> - and β-blocking properties), bradycardia<br>CIs: Iodine hypersensitivity, hyperthyroidism, third-degree AV heart block<br>PK: Half-life 58 days (average)<br>Inhibits CYP3A4/2D6/2C9/1A2/2C19 and intestinal P-gp<br>Substrate CYP3A4/1A2/2C19/2D6<br>DIs: Warfarin, digoxin, statins (maximum simvastatin dose 20 mg/day), phenytoin ↑ ≥ 50%, lidocaine, and others<br>Does not increase mortality in patients with HF | AF conversion:<br>IV: 5–7 mg/kg IV over 30–60 min, then 1.2–1.8 g/day continuous IV or divided oral doses until 10 g<br>PO: 1.2–1.8 g/day in divided doses until 10 g<br>AF maintenance: 200–400 mg/day PO<br>Pulseless VT/VF conversion:<br>300 mg or 5 mg/kg IVB in 20 mL of D <sub>5</sub> W or NS; repeat 150 mg IVB every 3–5 min<br>Stable VT: 150 mg IVB in 100 mL of D <sub>5</sub> W for 10 min<br>VT/VF maintenance: 1 mg/min × 6 hr, then 0.5 mg/min (maximum 2.2 g/day) |
| Sotalol<br>(Betapace,<br>Betapace AF)  | AEs: ADHF, bradycardia, AVB, wheezing, 3%–8% TdP within 3 days of initiation, bronchospasm (β-blocking effects)<br>CIs: Baseline QTc > 440 ms or CrCl < 40 mL/min/1.73 m <sup>2</sup> (AF only), LVEF < 40%<br>PK: Renally eliminated, half-life 30–40 hr<br>Hospitalization ideal for initiation of therapy because of BW: Do not initiate if baseline QTc interval > 450 ms; if QTc > 500 ms during therapy, reduce the dose, prolong the infusion duration, or d/c use<br>Not effective for AF conversion  | AF maintenance (based on CrCl):<br>80 mg PO BID (> 60 mL/min/1.73 m <sup>2</sup> )<br>80 mg PO daily (40–60 mL/min/1.73 m <sup>2</sup> )<br>CI < 40 mL/min/1.73 m <sup>2</sup><br>VT maintenance (based on CrCl):<br>80 mg PO BID (> 60 mL/min/1.73 m <sup>2</sup> )<br>80 mg PO daily (30–60 mL/min/1.73 m <sup>2</sup> )<br>80 mg PO every 36–48 hr (10–30 mL/min)<br>80 mg PO: individualize; every 48 hr minimum (< 10 mL/min/1.73 m <sup>2</sup> )                             |

**Table 19.** Antiarrhythmic Drug Properties and Dosing (class I and III agents only) (Cont'd)

| Drug   | AEs, Contraindications, Pharmacokinetics, and Drug Interactions  | Dosing by Indication  |
|--|--|---|
| <b>Class III: K<sup>+</sup> channel blockers</b> |  |   |
| Dofetilide<br>(Tikosyn)                          | AEs: TdP (0.8%; 4% if no renal adjustment), diarrhea<br>CIs: Baseline QTc > 440 ms or CrCl < 20 mL/min/1.73 m <sup>2</sup><br>PK: Renal and hepatic elimination<br>Half-life 6–10 hr<br>Substrate CYP3A4<br>DIs: CYP3A4 inhibitors and drugs secreted by kidney (cimetidine, ketoconazole, verapamil, trimethoprim, prochlorperazine, megestrol), HCTZ<br>BW: Hospitalization mandatory for initiation, obtain QTc 2–3 hr after each of the first 5 doses, reduce 50% if QTc ↑ > 15%; NTE QTc > 500 ms<br>Does not increase mortality in patients with HF  | AF conversion (based on CrCl; efficacy 12% at 1 mo):<br>500 mcg PO BID (> 60 mL/min/1.73 m <sup>2</sup> )<br>250 mcg PO BID (40–60 mL/min/1.73 m <sup>2</sup> )<br>125 mcg PO BID (20–40 mL/min/1.73 m <sup>2</sup> )<br>CI < 20 mL/min/1.73 m <sup>2</sup><br>AF maintenance: Dose as above according to renal function; adjust for QTc NTE 500 ms or > 15% ↑ in QTc   |
| Ibutilide<br>(Corvert)                           | AEs: TdP 8%, AV heart block (β-blocking properties)<br>CIs: Baseline QTc > 440 ms, LVEF < 30%, concomitant antiarrhythmic drugs<br>PK: Half-life 2–12 hr (average 6)<br>DIs: CYP3A4 inhibitors or QT-prolonging drugs<br>ECG monitoring during and 4 hr after CV   | AF conversion: 1 mg IV (≥ 60 kg) or 0.01 mg/kg IV (< 60 kg); repeat in 10 min if ineffective (efficacy 47% at 90 min)<br>BW: Potentially fatal arrhythmias (e.g., polymorphic VT) can occur with ibutilide, usually in association with TdP; patients with chronic AF may not be the best candidates for ibutilide conversion   |
| Dronedarone<br>(Multaq)                          | AEs: Worsening HF, QT prolongation, hypokalemia or hypomagnesemia with K <sup>+</sup> -sparing diuretics, hepatic failure<br>CIs: QTc ≥ 500 ms or PR ≥ 280 ms, NYHA class IV HF or NYHA class II–III HF with recent ADHF, severe hepatic impairment, second- or third-degree AVB, or HR < 50 beats/min<br>PK: Half-life 13–19 hr<br>Substrate 3A4<br>Inhibitor intestinal P-gp<br>DIs: CYP3A4 inhibitors, QT-prolonging drugs, simvastatin, tacrolimus/sirolimus, warfarin, and other CYP3A4 substrates with narrow therapeutic range, digoxin and other P-gp substrates (dabigatran, rivaroxaban) | AF maintenance:<br>400 mg orally BID<br>D/C if QTc is ≥ 500 ms<br>BW: The risk of death is doubled when used in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; use is contraindicated in these patients<br>Use in patients with permanent AF doubles the risk of death, stroke, and hospitalization for HF; use is contraindicated in patients with AF who will not or cannot be converted to normal sinus rhythm |

<sup>a</sup>Indicates that pill-in-pocket approach can be used for selected patients.

AF = atrial fibrillation; AV = atrioventricular; AVB = atrioventricular block; BW = Boxed Warning CAD = coronary artery disease; CI = contraindication; CNS = central nervous system; CR = controlled release; CV = cardioversion; D<sub>5</sub>W = dextrose 5%; DI = drug interaction; DOC = drug of choice; GI = gastrointestinal; HCl = hydrochloride; HCTZ = hydrochlorothiazide; IR = immediate release; LVH = left ventricular hypertrophy; ms = millisecond(s); NAPA = *N*-acetylprocainamide; NS = normal saline; NTE = not to exceed; NYHA = New York Heart Association; PK = pharmacokinetics; QTc = corrected QT interval; SR = sustained release; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia.

## E. Long-term Management of Ventricular Arrhythmias

### 1. Nonsustained VT

#### a. Asymptomatic

- Infrequent ventricular ectopic beats, couplets, and triplets without other signs of underlying structural heart disease (SHD) or inherited arrhythmia syndrome should be considered a normal variant in asymptomatic patients.

- ii. No treatment other than reassurance is needed for patients without SHD or inherited arrhythmia disorder.
- iii. Treat survivors of MI and HF with reduced EF with  $\beta$ -blockers (class I) unless contraindicated.
- b. Symptomatic
  - i.  $\beta$ -Blockers may be considered for a therapeutic trial in symptomatic patients (class IIb, level of evidence [LOE] C).
  - ii. Non-dihydropyridine CCBs may be considered as an alternative to  $\beta$ -blocker therapy in suitable patients without SHD.
  - iii. Antiarrhythmic drug (AAD) therapy (amiodarone, flecainide, mexiletine, propafenone, sotalol) may be considered to improve symptoms associated with arrhythmias in patients on adequate doses of  $\beta$ -blocker or CCB (class IIb; LOE C).
    - (a) Flecainide and propafenone are not recommended to suppress premature ventricular contractions in patients with reduced LV function (class III).
    - (b) Sotalol should be used with caution in patients with chronic kidney disease and should be avoided in patients with prolonged QT interval at baseline or excessive prolongation of QT interval (500 milliseconds) on therapy initiation (class I; LOE B).
    - (c) Amiodarone appears to have less overall proarrhythmic risk than other AADs in patients with HF and may be preferred to other membrane-active AADs unless functioning defibrillator has been implanted (class IIb; LOE C).
  - iv. Amiodarone, sotalol, and other  $\beta$ -blockers are useful after defibrillator implantation to reduce shocks and to suppress nonsustained VT in patients who are unsuitable for ICD therapy, in addition to optimal medical therapy for patients with HF.
- 2. Sustained VT
  - a. Immediate defibrillation (advanced CV life support management)
  - b. Evaluate cardiac structure and function.
  - c. ICDs indicated for most patients with SHD

#### F. Implantable Cardioverter-Defibrillators

- 1. For primary prevention of SCD
  - a. Previous MI, at least 40 days earlier and EF of 35% or less
  - b. Nonischemic dilated cardiomyopathy, LVEF of 35% or less receiving optimal chronic medications for at least 3 months
  - c. Syncope with SHD and inducible VT/VF during electrophysiological study
  - d. High risk of life-threatening VT/VF; congenital long QT syndrome with recurrent symptoms or torsades de pointes while receiving  $\beta$ -blocker
  - e. Must have reasonable survival expectation for more than 1 year
- 2. For secondary prevention of SCD
  - a. Previous episode of resuscitated VT/VF, hemodynamically unstable VT with no completely reversible cause, or sustained VT in presence of heart disease
  - b. Must be receiving optimal chronic medications ( $\beta$ -blockers, ACE inhibitors)
  - c. Must have reasonable survival expectation for more than 1 year
- 3. General medication considerations with ICD (Table 19)
  - a.  $\beta$ -Blockers
    - i. Considered mainstay therapy
    - ii. Effective in suppressing ventricular ectopic beats and in reducing SCD in a spectrum of cardiac disorders in patients with and without HF (nonsustained VT)

- b. Amiodarone
  - i. No better than ICD in reducing SCD as a lone agent; no mortality benefit
  - ii. Can be used to treat symptomatic nonsustained VT if  $\beta$ -blockers not effective when ICD not indicated
  - iii. Can be used in combination with  $\beta$ -blockers to decrease firing of ICD (defibrillator storm)
- c. Sotalol
  - i. No mortality advantage
  - ii. Can suppress VT and be used to decrease frequency of ICD firing
  - iii. Greater proarrhythmic potential; avoid in patients with severely depressed LVEF or significant HF; renal dosing necessary

**Table 20.** Alteration of Defibrillation Threshold

| Threshold Alteration | Medications                           | Comments  |
|----------------------|---------------------------------------|---|
| Increase threshold   | Amiodarone, lidocaine, and mexiletine | Reprogram ICD, increased energy (joules) needed |
| Decrease threshold   | Sotalol                               | May decrease energy needed for DCC              |

DCC = direct current conversion; ICD = implantable cardioverter-defibrillator.

#### G. Treatment of Arrhythmias in Special Patient Populations

- 1. HF
  - a. Avoid class Ia and class Ic agents.
  - b. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after MI.
  - c. Dronedarone (used in atrial arrhythmias only) is contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; risk of death was doubled in these patients.
- 2. Acute MI
  - a. Avoid class Ia and class Ic agents.
  - b. CAST trial with class Ic agents (encainide, flecainide) showed greater mortality when used to treat post-MI non-life-threatening ventricular arrhythmias; avoid class Ic agents in patients with SHD.
  - c. Class Ia medications: Increased mortality in MI survivors
  - d. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after MI.

#### H. Drug-Induced Arrhythmias: Review all potential drug etiologies and treat appropriately.

- 1. Drug-induced QT prolongation
  - a. Discontinue offending agent if QT prolongation significant (i.e. > 450 msec)
  - b. Ensure proper renal and hepatic dosing adjustments.
  - c. Review electrolyte abnormalities and thyroid function tests.
  - d. Ensure that all electrolytes are maintained at critical levels:  $K^+$  greater than 4 mmol/L and less than 5 mmol/L and  $Mg^{++}$  greater than 2 mg/dL.
  - e. Ensure that all ECG parameters are within normal limits (e.g., QT interval less than 500 milliseconds).
- 2. Drug-induced bradycardia or atrioventricular block
  - a.  $\beta$ -Blocker, CCB, digoxin
  - b. Administer antidote if appropriate (e.g., calcium for CCB toxicity).
- 3. Review for drug interactions. Antiarrhythmic agents have drug interactions that may cause significant outcomes.

**Patient Cases**

*Questions 8 and 9 pertain to the following case.*

A 68-year-old man is admitted after an episode of syncope, with a presyncopal syndrome of seeing black spots and experiencing dizziness before passing out. Telemetry monitor showed sustained VT for 45 seconds. His medical history includes HF NYHA class III, LVEF 30%, two MIs, hypertension for 20 years, LV hypertrophy, DM, and diabetic nephropathy. His medications include lisinopril 5 mg/day, furosemide 20 mg twice daily, metoprolol 25 mg twice daily, digoxin 0.125 mg/day, glyburide 5 mg/day, and aspirin 81 mg/day. His blood pressure is 120/75 mm Hg, heart rate 80 beats/minute, BUN 30 mg/dL, and SCr 2.2 mg/dL.

8. Which is the best therapy to initiate for conversion of his sustained VT?
  - A. Amiodarone 150 mg intravenously for 10 minutes, then 1 mg/minute for 6 hours, then 0.5 mg/minute.
  - B. Sotalol 80 mg twice daily titrated to QTc of about 450 milliseconds.
  - C. Dofetilide 500 mcg twice daily titrated to QTc of about 450 milliseconds.
  - D. Procainamide 20 mg/minute, with a maximum of 17 mg/kg.
  
9. The patient presents to the emergency department 3 months after amiodarone maintenance initiation (he refused ICD placement) after a syncopal episode, during which he lost consciousness for 30 seconds, according to witnesses. He also has rapid heart rate episodes during which he feels dizzy and light-headed. He feels very warm all the time (he wears shorts, even though it is winter), is unable to sleep, and has experienced a 3-kg weight loss. He received a diagnosis of hyperthyroidism caused by amiodarone therapy. On telemetry, he shows runs of nonsustained VT. Which would best predict the duration of amiodarone-associated hyperthyroidism in this patient?
  - A. Never.
  - B. 1 month.
  - C. 6 months.
  - D. 1 year.
  
10. A 64-year-old woman presents to the emergency department with the chief concern of palpitations. Her medical history includes hypertension controlled with a diuretic and an inferior-wall MI 6 months ago. She is pale and diaphoretic, but she can respond to commands. The patient's laboratory values are within normal limits. Her vital signs include blood pressure 95/70 mm Hg and heart rate 145 beats/minute; telemetry shows sustained VT. Although initially unresponsive to  $\beta$ -blockers, the patient is successfully treated with lidocaine. Subsequent electrophysiological testing reveals inducible VT, and sotalol 80 mg orally twice daily is prescribed. Two hours after the second dose, the patient's QTc is 520 milliseconds. Which regimen change would be most appropriate for this patient?
  - A. Continue sotalol at 80 mg orally twice daily.
  - B. Increase sotalol to 120 mg orally twice daily.
  - C. Discontinue sotalol and initiate dofetilide 125 mcg orally twice daily.
  - D. Discontinue sotalol and initiate amiodarone 400 mg orally three times daily.

## IV. HYPERTENSIVE CRISES

### A. Definitions

1. Hypertensive emergency
  - a. Severe elevations in blood pressure (usually greater than 180/120 mm Hg) with evidence of new or worsening target-organ damage
  - b. Acute target-organ damage can include hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke or other acute neurological deficit; unstable angina or acute MI; acute LV failure with pulmonary edema; dissecting aortic aneurysm; retinopathy or papilledema; decreased urinary output or acute renal failure; eclampsia.
  - c. Actual blood pressure may not be as important at the rate of blood pressure rise.
  - d. Requires immediate blood pressure lowering (not necessarily to normal ranges) to prevent or limit further target-organ damage
  - e. In general, oral therapy is discouraged for hypertensive emergencies.
2. Hypertensive urgency
  - a. Situations associated with severe blood pressure elevation in otherwise stable patients without acute or impending change in target-organ damage or dysfunction
  - b. Short-term risk is not as high; therefore, blood pressure reduction occurs over several days, not immediately.

### B. Goals and Treatment

1. Hypertensive emergency
  - a. Goal is to minimize target-organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.
  - b. Patients are usually admitted for intensive care unit care and close follow-up.
  - c. Lower mean arterial pressure (MAP) by no more than 25% or diastolic blood pressure to 100–110 mm Hg within first hour, then/100 mm Hg over next 2–6 hours, then to normal over next 24–48 hours.
  - d. Compelling conditions requiring rapid lowering of SBP, usually to less than 140 mm Hg, in the first hour of treatment include aortic dissection, severe preeclampsia or eclampsia, and pheochromocytoma with hypertensive crisis.
  - e. Intravenous medications used commonly (Table 21)
  - f. No randomized evidence to suggest one drug of choice because of small trial size, lack of long-term follow-up, and failure to report outcomes
  - g. Two trials have shown that nicardipine is better than labetalol in achieving the short-term blood pressure target.
  - h. Agents are chosen on the basis of drug pharmacology, pathophysiological factors underlying the patient's hypertension, degree of progression of target-organ damage, desirable rate of blood pressure decline, and presence of patient characteristics (Table 21-22).
  - i. No randomized evidence exists comparing different strategies to reduce blood pressure, except in patients with intracranial hemorrhage.
  - j. No randomized evidence suggests how rapidly to reduce blood pressure.
  - k. Clinical experience indicates that excessive reductions in blood pressure can cause renal, cerebral, or coronary ischemia and should be avoided.
1. Oral loading doses of antihypertensive agents can bring about cumulative effects, causing hypotension after discharge.

2. Hypertensive urgency
  - a. Treated by reinstitution or intensification of antihypertensive drug therapy
  - b. No indication for referral to the emergency department, immediate reduction in blood pressure in the emergency department, or hospitalization
  - c. No proven benefit exists from rapid reduction in blood pressure.
  - d. The choice of agent used in this setting varies, and in many cases, adjusting chronic oral therapy (increasing doses), reinitiating therapy in the nonadherent, or adding a new agent (i.e., diuretic) to long-term therapy is appropriate.
  - e. All patients with hypertensive urgency should be reevaluated within 7 days (preferably after 1–3 days).

C. Treatment Options (Table 21)

**Table 21.** Commonly Used IV Drugs for Hypertensive Emergencies

| Drug (onset, duration)                                    | IV Dose   | Comments/AEs  |
|---|---|---|
| <b>Vasodilators</b>                                       |   |   |
| Sodium nitroprusside<br>(Nipride)<br>(immediate, 2–3 min) | 0.3–0.5 mcg/kg/min, increase in increments of 0.5 mcg/kg/min to achieve BP target; maximum 10 mcg/kg/min; for infusion rates $\geq$ 4–10 mcg/kg/min or duration $>$ 30 min, thiosulfate can be coadministered to prevent cyanide toxicity | Intra-arterial BP monitoring recommended to prevent “overshoot”; lower doses required in older adult patients; tachyphylaxis common with extended use<br><br>AEs: Cyanide or thiocyanate toxicity with prolonged use can result in irreversible neurological changes and cardiac arrest, nausea, vomiting, methemoglobinemia<br><br>CIs: Renal, hepatic failure<br><br>Caution: Elevated ICP                          |
| Nitroglycerin<br>(2–5 min, 5–10 min)                      | 5–10 mcg/min, increase in increments of 5 mcg/min every 3–5 min to a maximum 20 mcg/min   | Use only in patients with ACS and/or acute pulmonary edema; do not use in volume-depleted patients<br><br>AEs: Headache, nausea, vomiting, tachyphylaxis  |
| Hydralazine<br>(Apresoline)<br>(10 min, 1–4 hr)           | 5–10 mg via slow IV infusion every 4–6 hr (NTE initial 20 mg/dose)  | BP begins to decrease within 10–30 min, and lasts 2–4 hr; unpredictability of response and prolonged duration of action make hydralazine less desirable first agent<br><br>AEs: Reflex tachycardia, headache, flushing<br><br>Caution: Angina or MI, elevated ICP, aortic dissection  |
| Enalaprilat<br>(Vasotec)<br>(within 30 min, 12–24 hr)     | 0.625–1.25 mg over 5 min; doses can be increased up to maximum 5 mg every 6 hr  | Should not be used in acute MI; mainly useful in hypertensive emergencies associated with hypertensive emergencies associated with high plasma renin activity; dose not easily adjusted; relatively slow onset (15 min) and unpredictability of BP response<br><br>AEs: Renal insufficiency or failure, hyperkalemia<br><br>CIs: Pregnancy, bilateral renal artery stenosis, angioedema<br><br>(Note: Long half-life) |

**Table 21.** Commonly Used IV Drugs for Hypertensive Emergencies (*Cont'd*)

| Drug (onset, duration)  | IV Dose  | Comments/AEs   |
|---|--|--|
| <b>Vasodilators</b>   |  |  |
| Fenoldopam<br>(Corlopam)<br><td>0.1–0.3 mcg/kg/min, increased by 0.05–0.1 mcg/kg/min every 15 min to a maximum of 1.6 mcg/kg/min</td> <td>Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy<br/>AEs: Headache, flushing, tachycardia, cerebral ischemia</td> | 0.1–0.3 mcg/kg/min, increased by 0.05–0.1 mcg/kg/min every 15 min to a maximum of 1.6 mcg/kg/min   | Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy<br>AEs: Headache, flushing, tachycardia, cerebral ischemia  |
| Nicardipine<br>(Cardene)<br>(1–5 min, 15–30 min; up to 4 hr if prolonged infusion)  | 5 mg/hr, increased by 2.5 mg/hr every 5 min to a maximum 15 mg/hr  | Contraindicated in advanced aortic stenosis; no dose adjustment needed for older patients<br>AEs: Reflex tachycardia, nausea, vomiting, headache, flushing<br>Caution: Angina or MI, acute HF  |
| Clevidipine<br>(Cleviprex)<br>(2–4 min, 5–15 min)   | 1–2 mg/hr, doubling every 90 s until BP approaches target, then increasing by less than double every 5–10 min; maximum 32 mg/hr; maximum duration 72 hr  | Patients with renal failure and hepatic failure and older adults not specifically studied—use low end range for older adults; contraindicated in soy or egg product allergy, severe aortic stenosis, defective lipid metabolism (e.g. pathological hyperlipidemia, lipoid nephrosis or acute pancreatitis)<br>Caution: HF, concomitant $\beta$ -blocker use, reflex tachycardia, rebound HTN |
| <b>Adrenergic Inhibitors</b>  |  |  |
| Esmolol<br>(Brevibloc)<br>(1–2 min, 10–30 min)  | LD 500–1000 mcg/kg IVB over 1 min, then a 50 mcg/kg/min infusion; for additional BP lowering, the bolus dose is repeated and the infusion is increased in 50 mcg/kg/min increments as needed to a maximum 200 mcg/kg/min | Contraindicated in patients with concurrent $\beta$ -blocker therapy, bradycardia, or decompensated HF<br>AEs: Bronchospasm, HF exacerbation, bradycardia or heart block<br>Caution: May worsen acute HF, asthma (higher doses may block $\beta_2$ receptors and impact lung function in reactive airway disease), heart block   |
| Labetalol<br>(Normodyne, Trandate)<br>(5–10 min, 3–6 hr)  | 20–80 mg every 15 min or initial 0.3–1 mg/kg dose (max 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/hr infusion up to maximum 3 mg/kg/hr   | Contraindicated in reactive airway disease or chronic obstructive pulmonary disease; especially useful in hyperadrenergic syndromes; may worsen HF and should not be given in patients with second- or third-degree heart block or bradycardia   |
| Phentolamine<br>(2 min, 15–30 min)  | IVB dose 5 mg; additional bolus doses every 10 min as needed   | Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, monamine oxidase inhibitors interactions with food and/or drugs, cocaine toxicity, amphetamine overdose, or clonidine withdrawal)  |

CI = contraindication; ICP = intracranial pressure.

**Table 22.** Agents Preferred for Hypertensive Crises According to Comorbidities

| Comorbidity   | Preferred Agents  | Comments   |
|---|---|--|
| Acute aortic dissection   | Labetalol, esmolol  | Requires rapid lowering of SBP to $\leq$ 120 mm Hg; $\beta$ -blocker should be given before vasodilator (nicardipine or nitroprusside) if needed for BP control or to prevent reflect tachycardia or inotropic effect; SBP $\leq$ 120 mm Hg should be achieved within 20 min   |
| Acute coronary syndromes  | Esmolol or nitroglycerin (preferred), labetalol, nicardipine                        | Nitrates given in the presence of PDE-5 inhibitors may induce profound hypotension; contraindications to $\beta$ -blockers include moderate to severe LV failure with pulmonary edema, bradycardia (< 60 beats/min), hypotension (SBP < 100 mm Hg), poor peripheral perfusion, second- or third-degree heart block, and reactive airway disease  |
| Acute pulmonary edema   | Clevidipine, nitroglycerin, nitroprusside   | $\beta$ -Blockers contraindicated  |
| Acute renal failure   | Clevidipine, fenoldopam, nicardipine  |  |
| Eclampsia or preeclampsia   | Hydralazine, labetalol, nicardipine   | Requires rapid BP lowering; ACE inhibitor, ARBs, renin inhibitors, and nitroprusside contraindicated   |
| Perioperative HTN (BP $\geq$ 160/90 mm Hg or SBP elevation > 20% of the preoperative value that persists > 15 min)      | Clevidipine, esmolol, nicardipine, nitroglycerin                                    | Intraoperative hypertension is most common during anesthesia induction and airway manipulation   |
| Acute sympathetic discharge or catecholamine excess states (e.g., pheochromocytoma, post-carotid endarterectomy status) | Clevidipine, nicardipine, phentolamine<br>(Note: Avoid unopposed $\beta$ -blockade) | Requires rapid lowering of BP  |
| Acute intracranial hemorrhage   | IV continuous infusion  | Lower BP in those who present with SBP > 220 mm Hg with continuous IV infusion and close BP monitoring; immediate lowering of SBP < 140 mm Hg is not of benefit and may be harmful   |
| Acute ischemic stroke   | No preference of agent  | Early initiation or resumption of antihypertensive treatment indicated only in (1) patients treated with tissue-type plasminogen activator to a SBP < 185/110 mm Hg and (2) patients with SBP > 220 mm Hg or DBP > 120 mm Hg; cerebral autoregulation in the ischemic penumbra of the stroke is grossly abnormal and rapid reduction of BP can be detrimental; reinitiate antihypertensive therapies in those with preexisting hypertension after neurological stability |

ARB = angiotensin receptor blocker.

**Patient Cases**

11. A 68-year-old man with a history of chronic kidney disease stage V on hemodialysis, hypertension, CAD post-MI, moderately depressed LVEF, and gastroesophageal reflux disease presents with acute-onset shortness of breath and chest pain. After his recent dialysis, he had a large barbecue meal with salt and smoked some marijuana laced with cocaine. He was nonadherent to medical therapy for 2 days and noticed he had gained 2 kg in 24 hours. His baseline orthopnea worsened to sleeping sitting up in a chair for the 2 nights before admission. He developed acute-onset chest tightness with diaphoresis and nausea, and his pain was 7/10. He went to the emergency department, where a blood pressure of 250/120 mm Hg was noted. He had crackles halfway up his lungs on examination, and chest radiography detected bilateral fluffy infiltrates with prominent vessel cephalization. Electrocardiography revealed sinus tachycardia, heart rate 122 beats/minute, and ST-segment depressions in leads 2, 3, and aVF. He was admitted for a hypertensive emergency. Laboratory results are as follows: BUN 48 mg/dL, SCr 11.4 mg/dL, BNP 2350 pg/mL, troponin T 1.5 mcg/L (less than 0.1 mcg/L), creatine kinase 227 units/L, and creatine kinase-MB 22 units/L. Which medication is best to manage this patient's hypertensive emergency?

- Intravenous nitroglycerin 5 mcg/minute titrated to a 25% reduction in MAP.
- Labetalol 2 mcg/minute titrated to a 50% reduction in MAP.
- Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.
- Clonidine 0.1 mg orally every 2 hours as needed for a 50% reduction in MAP.

12. A 56-year-old white woman with a long history of hypertension because of nonadherence and recently diagnosed HF (EF 35%) presents to the local emergency department with a blood pressure of 210/120 mm Hg and heart rate of 105 beats/minute. She states that she felt a little light-headed but that she now feels okay. She ran out of her blood pressure medications (including hydrochlorothiazide, carvedilol, and lisinopril) 3 days ago. Current laboratory values are within normal limits. Which medication is best for this patient?

- Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.
- Labetalol 80 mg intravenously; repeat until blood pressure is less than 120/80 mm Hg.
- Resumption of home medications; refer for follow-up within 2 days.
- Resumption of home medications; initiate amlodipine 10 mg daily; refer for follow-up in 1 week.

**V. PULMONARY HYPERTENSION**

- Definition, Diagnosis, and Treatment Goals
  - Pulmonary hypertension (PH)
    - A hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (mPAP) of 25 mm Hg or greater at rest as assessed by right heart catheterization
    - PH can be found in many clinical conditions.
    - Current clinical classification
      - Individualizes different categories of PH sharing similar pathological and hemodynamic characteristics (Table 23)
      - Used by the FDA and European Agency for Drug Evaluation for new drugs approved for PH

**Table 23.** Clinical Classification of PH

| Category of PH | Clinical Characteristics   |
|----------------|--|
| Group 1        | PAH; pathological lesions affect the distal pulmonary arteries in particular   |
| Group 2        | PH caused by left heart disease; pathologic changes are characterized by enlarged and thickened pulmonary veins, pulmonary capillary dilatation, interstitial edema, alveolar hemorrhage, and lymphatic vessel and lymph node enlargement  |
| Group 3        | PH caused by chronic lung disease or hypoxia; pathological changes include medial hypertrophy and intimal obstructive proliferation of the distal pulmonary arteries   |
| Group 4        | CTEPH; pathological lesions are characterized by organized thrombi tightly attached to the pulmonary arterial medial layer in the elastic pulmonary arteries, replacing the normal intima; nonoccluded areas may be indistinguishable from PAH; collateral vessels can grow to reperfuse at least partly the areas distal to complete obstructions |
| Group 5        | PH caused by unclear multifactorial mechanisms   |

CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

2. Symptoms
  - a. Dyspnea with exertion (60% of patients), fatigue, chest pain, syncope, weakness (40%); caused by impaired oxygen delivery to tissues and diminished CO
  - b. Orthopnea, peripheral edema, liver congestion, abdominal bloating, and other signs of right ventricular hypertrophy and failure occur when disease progresses to involve the heart.
3. Diagnosis and classification: Severity of disease should be evaluated in a systemic and consistent manner through a combination of clinical and functional classifications (Tables 23–25), exercise capacity, and echocardiographic, laboratory, and hemodynamic variables to inform therapeutic decisions.

**Table 24.** Diagnostic Findings of PAH

| Type                    | Diagnostic Findings  |
|-------------------------|--|
| Hemodynamic alterations | mPAP $\geq$ 25 mm Hg at rest, PAWP $\leq$ 15 mm Hg, and PVR $>$ 3 Wood units on RHC  |
| ECG                     | Signs of RV hypertrophy, right-axis deviation, and anterior ST- and T-wave abnormalities consistent with RV strain pattern |
| Echocardiography        | Estimated RV systolic pressure elevation, enlarged RV, RV dysfunction  |
| Chest radiography       | Enlarged pulmonary arteries and diminished peripheral pulmonary vascular markings, RV enlargement                          |
| Physical examination    | Cool or cyanotic extremities, jugular venous distension, pulsatile hepatomegaly, peripheral edema, ascites                 |

mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RV = right ventricle.

**Table 25.** World Health Organization Classification of Functional Status for PAH

| Class | Definition  |
|-------|---|
| I     | No symptoms (dyspnea, fatigue, syncope, chest pain) with normal daily activities  |
| II    | Symptoms with strenuous normal daily activities that slightly limit functional status and activity level                                    |
| III   | Symptoms of dyspnea, fatigue, syncope, and chest pain with normal daily activities that severely limit functional status and activity level |
| IV    | Symptoms at rest; cannot conduct normal daily activities without symptoms   |

4. Treatment goals
  - a. Relieve acute dyspnea symptoms.
  - b. Improve exercise capacity and quality of life and prevent death.
5. Acute vasodilator response testing
  - a. Mandatory in patients with idiopathic pulmonary arterial hypertension (PAH) to identify those who will respond favorably to long-term treatment with high doses of CCBs
  - b. Inhaled nitric oxide is the compound of choice.
  - c. Intravenous epoprostenol and intravenous adenosine are alternatives but carry risk of systemic vasodilatory effects.
  - d. Positive response: mPAP reduction of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg
  - e. Positive response predicts mortality reduction with long-term CCB or vasodilator use.

B. Treatment of PAH (Boxes 4 and 5; Table 26-27)

1. All patients with PAH should be evaluated promptly at a center with expertise in the diagnosis of PAH before initiation of therapy.
2. Collaborative and closely coordinated care of patients with PAH should involve the expertise of the local physician and those with expertise in PAH care.
3. Treatment decisions are based on World Health Organization functional classification, prior treatment status, response to CCBs, and mode of administration desired.
4. Use of PAH drugs, particularly tested in clinical trials with PAH, might not be helpful in other forms of PH.
5. Use of PAH drugs in other forms of PH should not be generalized; treatment decisions must be made on an individual basis.

**Box 4. Initial PAH Treatment Algorithm: Supportive Care**

Supportive care: Treat corrective causes of hypoxemia and avoid dehydration, pain, fatigue, high altitude, smoking, pregnancy, and iron deficiency

Oxygen to maintain  $\text{Sao}_2 > 90\%$ , diuretic if peripheral edema or ascites

Oral anticoagulation, warfarin (INR 1.5–2.5) if IPAH  $\pm$  diuretics  $\pm$  digoxin

(Anticoagulation to prevent catheter thrombosis [IV prostaglandin use] and venous thromboembolism)

(IPAH, heritable PAH, and PAH caused by anorexigenics [class IIa; LOE C], APAH)

Immunizations for influenza and *Pneumococcus* spp.

Discuss effective methods of birth control with women of childbearing potential

Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

APAH= associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; LOE = level of evidence; PAH = pulmonary arterial hypertension.

**Box 5. PAH Treatment Algorithm: Vasoreactive Algorithm**

Positive response to acute vasoreactivity testing

Initiate oral CCB (WHO FC I-II)

If sustained response, continue CCB

If no sustained response, initiate non-vasoreactive algorithm in Table 26

CCB = calcium channel blocker; WHO FC = World Health Organization functional classification.

**Table 26.** PAH Treatment Algorithm: Non-vasoreactive Algorithm

| Negative response to acute vasoreactivity testing (or unresponsive to CCB therapy)  |          |   |  |   |
|---|----------|---|--|---|
| Initiate therapy with approved medications  |          |   |  |   |
| Recommendation  | Evidence | WHO FC II   | WHO FC III   | WHO FC IV   |
| I   | A or B   | Ambrisentan<br>Bosentan<br>Macitentan <sup>a,b,c</sup><br>Riociguat <sup>a</sup><br>Sildenafil<br>Tadalafil | Ambrisentan<br>Bosentan<br>Epoprostenol IV <sup>c</sup><br>Iloprost inhaled<br>Macitentan <sup>a,b,c</sup><br>Riociguat <sup>a</sup><br>Sildenafil<br>Tadalafil<br>Treprostинil SC, inhaled <sup>a</sup> | Epoprostenol IV <sup>c</sup>  |
| IIa   | C        |   | Iloprost IV + treprostинil IV  | Ambrisentan<br>Bosentan<br>Iloprost inhaled and IV <sup>a</sup><br>Macitentan <sup>a,b,c</sup><br>Riociguat <sup>a</sup><br>Sildenafil<br>Tadalafil<br>Treprostинil SC, IV, inhaled |
| IIb   | B        |   | Beraprost <sup>a</sup>   |   |
|   | C        |   | Initial combination therapy  | Initial combination therapy   |
| <p>If inadequate clinical response:</p> <p>Consider eligibility for lung transplantation</p> <p>Sequential combination therapy with ERAs, prostacyclins, PDE-5 inhibitor, or soluble guanylate cyclase stimulator</p> |          |   |  |   |
| <p>If inadequate response on maximal therapy:</p> <p>Referral for lung transplantation (class I)</p> <p>BAS (IIa; LOE C)</p>  |          |   |  |   |

Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

<sup>a</sup>Approved only by the U.S. Food and Drug Administration (macitentan, riociguat, treprostинil inhaled), in New Zealand (ilo-prost IV), and in Japan and South Korea (beraprost).

<sup>b</sup>Received positive opinion for approval by the European Medicines Agency.

<sup>c</sup>Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined).

BAS = balloon atrial septostomy; CCB = calcium channel blocker; ERA = endothelin receptor antagonist; PDE-5 = phosphodiesterase type 5; WHO FC = World Health Organization functional classification.

**Table 27.** Overview of Pulmonary Arterial Hemorrhage Treatment Options

| Drug, Mechanism, and Indication                                      | Dose   | Adverse Effects  | Considerations   |
|--|--|--|--|
| CCBs<br>Class II PAH   | Varies by agent and patient tolerance  | Hypotension, headache, dizziness, peripheral edema, cardiac conduction delay (diltiazem)   | Should not be used empirically without positive response to acute vasodilatory response testing<br>Diltiazem, amlodipine, nifedipine most commonly used<br>Select agent on the basis of HR at baseline<br>If tachycardic, choose diltiazem<br>If bradycardic, choose amlodipine, nifedipine  |
| Epoprostenol<br>(Flolan, Veletri)<br>Prostanoid<br>Class III–IV PAH  | 2–40 ng/kg/min IV  | Jaw pain, nausea, vomiting, flushing, headache, muscle aches and pain, catheter-related thrombosis, and IV line infections; rebound worsening of symptoms if abruptly discontinued | Continuous IV infusion by pump<br>Flolan: Unstable at acidic pH and room temperature (refrigerate or use ice packs before and during infusion)<br>Veletri: Stable at room temperature<br>Drug must be reconstituted in sterile environment<br>Medical emergency if infusion interrupted (half-life, 6 min); spare drug cassette and infusion pump should be kept available |
| Treprostинil<br>(Remodulin, Tyvaso)<br>Prostanoid<br>Class II–IV PAH | 1.25–40 ng/kg/min SC infusion, IV<br>Inhaled   | Severe erythema and induration (83%) and injection site pain (85%) limits use; also headache, nausea, diarrhea, rash   | Longer half-life (3 hr); longer to seek medical attention<br>Premixed, prefilled syringe easier to administer<br>Local treatments (hot/cold packs or topical analgesics) can be used to minimize infusion site discomfort<br>Moving infusion site every 3 days minimizes irritation  |
| Inhaled iloprost<br>(Ventavis)<br>Prostanoid<br>Class III–IV PAH     | 2.5 mcg × 1; then 5 mcg/inhalation by nebulizer 6–9 times daily while awake  | Mild, transient cough, flushing, headache, syncope   | 6–9 inhalations daily (15 min each with jet nebulizer)<br>Prodose AAD nebulization system required<br>Inhaled form has fewer systemic adverse reactions<br>Use no more than every 2 hr   |
| Oral treprostинil<br>(Orenitram)<br>Prostanoid                       | 0.25 mg every 12 hr or 0.125 mg every 8 hr; may increase dose in increments of 0.25 mg or 0.5 mg every 12 hr or 0.125 mg every 8 hr every 3–4 days as tolerated to achieve optimal clinical response | Limb pain (14%), hypokalemia (9%), abdominal distress (6%)   | Administer with food<br>Swallow tablets whole; do not crush, split, or chew; use only intact tablets<br>Dose reduction in moderate hepatic impairment<br>Contraindicated in severe hepatic impairment (Child-Pugh class C)<br>Alcohol increases absorption of treprostинil   |

**Table 27.** Overview of Pulmonary Arterial Hemorrhage Treatment Options (Cont'd)

| Drug, Mechanism, and Indication   | Dose                          | Adverse Effects   | Considerations  |
|---|-------------------------------|---|---|
| Bosentan (Tracleer)<br>Nonselective endothelin receptor antagonist (ET <sub>A</sub> and ET <sub>B</sub> )<br>Class III–IV PAH | 62.5–125 mg PO BID            | Peripheral edema 5%–14%, hypotension 7%, increased LFTs 11%, flushing 7%–14%, palpitations 5%               | Available only through REMS<br>Severe drug interactions with glyburide (increased LFTs) and cyclosporine (decreased efficacy of both cyclosporine and bosentan)<br>Monitor LFTs monthly<br>Monitor Hgb and Hct every 3 mo<br>Potential teratogen; if childbearing age, use two contraceptive methods (reduced efficacy of hormonal contraceptives); monthly pregnancy test needed<br>Efficacy decreased with inducers and toxicity increased with inhibitors of CYP 2C8/9 and 3A4   |
| Ambrisentan (Letairis)<br>Selective endothelin receptor antagonist (ET <sub>A</sub> only)<br>Class II–III PAH                 | 5–10 mg PO once daily         | Peripheral edema 17%, hypotension 0%, increased LFTs 0%–2.8%, flushing 4%, palpitations 5%, fluid retention | Available only through REMS<br>Caution with cyclosporine; maximum dose is 5 mg daily<br>Contraindicated in patients with idiopathic pulmonary fibrosis<br>Potential teratogen (see above comments)<br>Periodic Hgb and Hct monitoring<br>No CYP drug interactions documented  |
| Macitentan (Opsumit)<br>Dual endothelin receptor antagonist<br>Class II–III PAH   | 10 mg once daily              | Anemia, nasopharyngitis, bronchitis, headache, influenza, urinary tract infection                           | Contraindicated in pregnancy; available only through REMS<br>Metabolized by CYP3A4; avoid use with strong CYP3A4 inhibitors<br>Monitor for elevations of aminotransferases, hepatotoxicity, liver failure, and anemia   |
| Sildenafil (Revatio)<br>PDE-5 inhibitor<br>Class II–IV PAH  | 20–80 mg PO three times daily | Headache, epistaxis, facial flushing, bluish or blurry vision, light sensitivity, dyspepsia, insomnia       | Half-life 4–5 hr<br>May augment effects of other vasodilators when used in combination (especially prostacyclin)<br>Contraindicated in patients receiving nitrates<br>Avoid combined use with strong CYP3A4 inhibitors (e.g., ritonavir, cimetidine, erythromycin) and inducers (rifampin)  |
| Tadalafil (Adcirca)<br>PDE-5 inhibitor<br>Class II–IV PAH   | 20–40 mg PO once daily        | Headache, flushing, indigestion, nausea, backache, myalgia, nasopharyngitis, respiratory tract infection    | Half-life 17.5 hr<br>May augment effects of other vasodilators when used in combination (especially prostacyclin)<br>Contraindicated in patients receiving nitrates<br>If CrCl = 31–80 mL/min/1.73 m <sup>2</sup> , initiate 20 mg PO once daily and titrate as tolerated<br>If CrCl < 30 mL/min/1.73 m <sup>2</sup> or hemodialysis, avoid use<br>If Child-Pugh class A or B, initiate 20 mg PO once daily and titrate as tolerated<br>If Child-Pugh class C, avoid use<br>Avoid use with potent CYP3A4 inhibitors or inducers |

**Table 27.** Overview of Pulmonary Arterial Hemorrhage Treatment Options (*Cont'd*)

| Drug, Mechanism, and Indication  | Dose   | Adverse Effects   | Considerations   |
|--|--|---|--|
| Riociguat (Adempas)<br>Soluble guanylate cyclase stimulator<br>Chronic thromboembolic PH and class II–IV PAH | 1 mg PO three times daily; increase by 0.5 mg no sooner than 2-wk intervals; maximum dose 2.5 mg three times daily   | Headache, dizziness, dyspepsia or gastritis, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation<br><br>Serious bleeding occurred in 2.4%, compared with 0% in placebo in clinical trials, including one fatal event | Contraindicated with nitrates; NO donors in any form or use with any PDE inhibitors (including nonspecific and specific PDE-5 inhibitors)<br><br>Teratogenic, contraindicated in pregnancy<br><br>Available only through restricted REMS program for women<br><br>Not recommended for patients with pulmonary veno-occlusive disease<br><br>Half-life: 7–12 hr<br><br>Plasma concentrations reduced in smokers<br><br>Drug interaction with strong CYP3A4 inhibitors and P-gp/breast cancer resistance protein; may use a lower starting dose of 0.5 mg three times daily; decrease dose by 0.5 mg if hypotension occurs<br><br>Not recommended in severe renal or hepatic disease ( $\text{CrCl} < 15 \text{ mL/min}/1.73 \text{ m}^2$ or Child-Pugh class C) |
| Ambrisentan/tadalafil combination<br>Class II–III PAH  | Initiate ambrisentan 5 mg once daily, with or without tadalafil 20 mg once daily<br><br>Increase to 20 mg ambrisentan or 40 mg tadalafil at 4-wk intervals | Most common: peripheral edema, headache, nasal congestion, cough, anemia, dyspepsia, and bronchitis   | Same considerations for each individual agent as above<br><br>REMS program<br><br>Do not split, crush, or chew tablets   |
| Selexipag (Uptravi)<br>Oral non-prostanoid prostacyclin IP receptor agonist<br>Class II–III PAH              | Initiate at 200 mcg BID; increase by 200 mcg BID at weekly intervals up to 1600 mcg BID reached  | Headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity and flushing   | Take with food to improve tolerability. Can cause pulmonary edema with pulmonary veno-occlusive disease. D/C treatment if confirmed<br><br>Strong CYP2C8 inhibitors should be avoided<br><br>Decrease dosing to once daily in patients with moderate hepatic impairment and avoid in patients with severe hepatic impairment<br><br>Not for use in breastfeeding   |

AAD = adaptive aerosol delivery; d/c = discontinue; ET = endothelin; Hct = hematocrit; Hgb = hemoglobin; LFT = liver function test; NO = nitric oxide; PAH = pulmonary artery hemorrhage; REMS = Risk Evaluation and Mitigation Strategies.

**Patient Cases**

13. A 38-year-old woman with obesity presents with increasingly severe symptoms of fatigue and shortness of breath. She could walk only 10–20 feet at baseline and is now short of breath at rest. Her arterial blood gas is pH 7.31,  $\text{PCO}_2$  65 mm Hg,  $\text{PO}_2$  53 mm Hg, and 85%  $\text{SaO}_2$ . She has three-pillow orthopnea and 3+ pitting edema in her lower extremities. Her medical history is significant only for AF. Computed tomographic angiography shows that her pulmonary artery trunk is substantially enlarged, with a mean pressure of 56 mm Hg. Echocardiography reveals right atrial and ventricular hypertrophy. Chest radiography detects prominent interstitial markings. Pertinent laboratory test values are BUN 21 mg/dL, SCr 1.2 mg/dL, AST 145 IU/L, alanine aminotransferase 90 IU/L, INR 2.1, and aPTT 52 seconds; vital signs include blood pressure 108/62 mm Hg and heart rate 62 beats/minute. Home medications are warfarin 2.5 mg/day, ipratropium 2 puffs every 6 hours, salmeterol 2 puffs twice daily, and diltiazem 480 mg/day. Her diagnosis is idiopathic pulmonary arterial hypertension (IPAH). Which regimen is the best evidence-based management strategy?

- A. Increase diltiazem to 600 mg/day.
- B. Start sildenafil 20 mg three times daily.
- C. Start epoprostenol 2 ng/kg/minute.
- D. Start bosentan 62.5 mg twice daily.

14. A 48-year-old man with IPAH is admitted to the medical intensive care unit for severe respiratory distress. Medications before admission included bosentan and sildenafil. His vital signs include blood pressure 97/45 mm Hg, heart rate 130 beats/minute, and respiratory rate 24 breaths/minute, and his oxygen requirements are increasing. Recently, during a previous hospital admission, pulmonary artery catheter placement revealed an mPAP of 40 mm Hg, right atrial pressure 16 mm Hg, CI 1.2 L/minute, and PCWP 15 mm Hg. Echocardiography reveals EF 60% with significant right ventricular dilation. Which regimen is most appropriate?

- A. Epoprostenol and add phenylephrine, if needed, for blood pressure support.
- B. Furosemide and add norepinephrine, if needed, for blood pressure support.
- C. Nitroprusside and add epinephrine, if needed, for blood pressure support.
- D. Dobutamine to increase CO.

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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: A**

This patient's atypical symptoms, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTE-ACS. She has at least three risk factors for CAD, a history of CAD (prior MI), and positive troponins, which places her at high risk of future events. In such high-risk patients, an early invasive strategy (as in Answers A and B) is used to determine whether occluded or partly occluded arteries exist, which ones can be intervened on, and whether to make an intervention. An ischemia-guided approach, also called *medical management*, as in Answers C and D, would not be preferred because of this patient's risk category (i.e., positive troponins). Dual antiplatelet therapy (aspirin plus a P2Y<sub>12</sub> inhibitor) is indicated for an early invasive strategy in the management of an NSTE-ACS. In patients undergoing PCI, clopidogrel, prasugrel, or ticagrelor is an appropriate option (Answer A is correct). After an initial bolus of 60 units/kg and an infusion of 12 units/kg/hour (Answer A is correct; Answer D is incorrect), UFH can be titrated to an aPTT of 50–70 seconds, making Answer A correct. Aspirin alone without a P2Y<sub>12</sub> agent, as in Answer B, would not provide adequate antiplatelet therapy. Furthermore, enoxaparin would need to be dosed with a 30-mg intravenous bolus before initiating twice-daily subcutaneous dosing because this patient has positive troponins. Glycoprotein inhibitors, as in Answer C, can be useful in high-risk patients, typically those with positive troponins; however, their benefit has been shown mainly when UFH, not low-molecular-weight heparin, is given as the anticoagulant.

**2. Answer: D**

It is important to understand that this patient case occurs in the context of elective stent placement, not after ACS. In the non-ACS setting, the duration of DAPT is determined by the type of stent placed (bare metal stent vs. drug-eluting stent). After elective drug-eluting stent placement, DAPT is recommended for at least 12 months because the risk of in-stent thrombosis is highest during this time. The recommendation is for at least 1 month—and ideally up to 1 year—after bare metal stent placement because endothelialization of the stent usually occurs early, typically within 1 month after stenting. Bleeding risk may be a reason to consider

earlier termination (after a minimum of 1 month) of DAPT after bare metal stent placement.

**3. Answer: D**

Although this patient presented within 3 hours of chest pain onset and is a candidate for thrombolytic therapy (within 6 hours of onset is preferred), up to 95% of patients can achieve normal, brisk TIMI-3 flow rates with primary PCI, compared with only 50%–60% of patients achieving normal TIMI-3 coronary flow with thrombolytic therapy. Because the patient presents to a hospital that can perform a primary PCI with stent implantation, this is the preferred reperfusion strategy (Answers B and C are incorrect). Answer A is incorrect because an anticoagulant agent must be administered in addition to antiplatelet therapy. Answer D—reperfusion with primary PCI, DAPT with aspirin and prasugrel, and dosing of bivalirudin as an anticoagulant strategy—is correct.

**4. Answer: C**

Unlike the patient in case 3, this patient presents with a STEMI to a rural community hospital where the nearest hospital with catheterization laboratory facilities is more than 120 minutes away (i.e., lytics are indicated). He presents within the window for fibrinolytic therapy consideration (less than 6 hours after chest pain onset) and has no obvious contraindications. Because he is still having ischemic chest pain and ST-segment elevation, he should benefit from reperfusion therapy. He is experiencing complete heart block and bradycardia, which could indicate an occlusion above the area perfusing his sinoatrial or atrioventricular nodes. Enoxaparin (Answer A) is a treatment option for anticoagulant therapy given in conjunction with fibrinolitics, but the patient is at higher risk of bleeding from impaired enoxaparin clearance and needs a dosage adjustment. Furthermore, he is older than 75 years, beyond the age at which the intravenous bolus should be given, and the alteplase dosing is incomplete. Simply treating this patient conservatively with UFH alone (Answer B) in the setting of ongoing chest pain, shortness of breath, and pulmonary edema is not optimal. Diagnostic catheterization and possible PCI to determine whether an artery can be reperfused (Answer D) may be desirable, but is complicated because the patient's SCr is elevated

(2.5 mg/dL), and he is in a rural hospital, where he cannot be assessed quickly enough (within 90–120 minutes). Because of the shorter half-life and ease of administration of tenecteplase, it may be preferable to alteplase. Clearance of UFH with tenecteplase is not as altered as with enoxaparin, and it would be a more appropriate therapy than enoxaparin in combination with a thrombolytic (Answer C is correct).

#### 5. Answer: C

This patient, who has ADHF, is receiving a  $\beta$ -blocker. Although long-term  $\beta$ -blockers can improve HF symptoms and reduce mortality, they can also worsen symptoms in the short term. It is recommended to keep the maintenance  $\beta$ -blocker therapy at the same or slightly lower dose compared with the outpatient therapy in patients with ADHF; increasing the  $\beta$ -blocker dose before reaching euvoolemia might acutely worsen his clinical picture (Answer A is incorrect). In patients admitted with volume overload without substantial signs of reduced CO, it is reasonable to try intravenous loop diuretics initially (Answer C is correct). As gut edema increases, oral loop diuretics (notably furosemide) become less effective because of decreased absorption. Nesiritide is a vasodilatory drug that is FDA approved for the symptomatic relief of acute HF; however, because of its lack of evidence for benefit, adverse effects, and substantial cost, nesiritide is not recommended for routine use in the broad population of patients with acute HF (Answer B is incorrect). Milrinone is an inotropic drug. Because of their adverse effects, inotropes are recommended in cold and wet exacerbations only after vasodilatory medications have failed (Answer D is incorrect).

#### 6. Answer: A

Intravenous vasodilators such as nitroglycerin (Answer A) and sodium nitroprusside (Answer B) are reasonable options if intravenous diuretics fail and the patient progresses to acute pulmonary edema. Both agents rapidly cause venous vasodilation and reduce pulmonary filling pressures, which can relieve acute shortness of breath. Answer A, nitroglycerin, is the optimal choice for this patient, given his declining renal function and the concern about increased risk of thiocyanate toxicity with sodium nitroprusside in this setting (Answer B is incorrect). Dobutamine is typically used in states of low CO decompensation and is counteracted by

concomitant  $\beta$ -blocker therapy, making it a poor choice in patients receiving  $\beta$ -blockers (Answer C is incorrect). Although milrinone is a more acceptable inotropic agent in a patient receiving  $\beta$ -blockers, the dosing strategy is inappropriate as an initial dose (Answer D is incorrect). Finally, inotropes are generally reserved for patients when other therapies have failed.

#### 7. Answer: A

Signs of a decreased CO state in HF (e.g., increased SCr, decreased mental status, cool extremities) suggest a cold and wet state, and adjunctive therapy is indicated. Positive inotropic agents such as milrinone will increase CO to maintain perfusion to vital organs. Milrinone will also vasodilate the peripheral vessels to unload the heart (lower SVR). Although dobutamine would be a potential choice in this patient, it is not recommended in patients receiving  $\beta$ -blockers (Answer B is incorrect). Although this patient has low blood pressure, his elevated SVR suggests that he will tolerate the vasodilatory effects of milrinone (Answer A is correct). Although nesiritide would provide venous and arterial vasodilation, it is relatively contraindicated in patients with a systolic blood pressure less than 100 mm Hg and is absolutely contraindicated in patients with a systolic blood pressure less than 90 mm Hg (Answer C is incorrect). Phenylephrine has no positive beta effects; therefore, it will not augment contractility. In addition, it will cause vasoconstriction through alpha stimulation, which will further increase SVR and probably worsen CO (Answer D is incorrect). Vasoconstrictors are reserved for patients in cardiogenic shock. Although this patient has signs of significant hypoperfusion, his blood pressure is not so low that it warrants vasopressor therapy.

#### 8. Answer: A

Treatment options for sustained VT depend on concomitant disease states, particularly LVEF (40% cutoff). In a patient with LV dysfunction, class I agents such as procainamide are contraindicated (Answer D is incorrect). In a patient whose CrCl is less than 60 mL/minute/1.73 m<sup>2</sup>, sotalol requires a considerable dose reduction to avoid excess risk of torsades de pointes. Sotalol is not an effective cardioversion drug but is more useful for preventing future episodes of arrhythmias (maintaining sinus rhythm) once sinus rhythm is achieved (Answer B is incorrect). Dofetilide is indicated only for AF, not

for ventricular arrhythmias; similarly, cardioversion rates with dofetilide are low (Answer C is incorrect). Amiodarone is first-line therapy for sustained VT in patients with severe renal insufficiency, HF, and structural heart disease (Answer A is correct).

#### **9. Answer: C**

With the prolonged half-life of amiodarone and extensive fat tissue volume of distribution, it would be expected that hyperthyroid adverse effects would last for 3–5 half-lives of the drug, which is anywhere from 5 to 8 months (Answer C is correct; Answer A is incorrect). Although therapeutic concentrations may fall off substantially by then, 1 month is too soon to expect the effects to subside (Answer B is incorrect). Although some iodine and amiodarone molecules will probably remain absorbed in fat stores for years, if not for life, therapeutic concentrations should not exist for longer than what is predicted by the half-life (Answer D is incorrect).

#### **10. Answer: D**

This patient is experiencing QT prolongation with sotalol, placing her at an elevated risk of developing life-threatening torsades de pointes. Sotalol should be discontinued immediately (Answer A and B are incorrect). Given the QT prolongation that occurred with sotalol, the same will probably occur with dofetilide (Answer C is incorrect). Amiodarone is associated with minimal risk of torsades de pointes and therefore would be an appropriate alternative agent to prevent ventricular arrhythmias (Answer D is correct).

#### **11. Answer: A**

Hypertensive emergency should be treated immediately by a 25% reduction in MAP, followed by a slow reduction to goal for 5–7 days. The patient's comorbidities guide the optimal therapy. His dialysis and SCr of 11.4 mg/dL are a contraindication to sodium nitroprusside (Answer C is incorrect) because of possible thiocyanate toxicity. Labetalol (and  $\beta$ -blockers in general) is controversial in patients who have taken cocaine, but its nonselective nature makes it an option; however, a reduction of 50% initially is too rapid a decrease in blood pressure for safety (Answer B is incorrect). Clonidine is not an appropriate drug for a hypertensive emergency because its oral form is difficult to titrate and can lead to precipitous drops in blood pressure

beyond the goal 25% reduction and possibly stroke or worsening MI (Answer D is incorrect). Nitroglycerin is an optimal choice, considering the patient's lack of contraindications to this therapy and his evolving MI (Answer A is correct).

#### **12. Answer: C**

In the setting of asymptomatic hypertensive crisis (without acute target-organ damage), giving intravenous medications, as in Answers A and B, and admitting the patient to the hospital are unnecessary (Answer A and B are incorrect). This patient is probably presenting because of a history of nonadherence. Resuming her home medications (Answer C is correct) at this time would be most appropriate, with close follow-up to ensure that her prescribed regimen is working. Adding a fourth agent (Answer D is incorrect) at this time is unnecessary, considering that she could be controlled on her current drug regimen if she were adherent. Follow-up should occur within the first few days rather than waiting 1 week.

#### **13. Answer: C**

This patient is already receiving therapy with CCBs to control her heart rate caused by AF. She is taking a large dose of diltiazem, and her heart rate is unlikely to tolerate further increases in therapy (Answer A is incorrect). Sildenafil is indicated for patients to improve symptoms or for patients whose other therapies have failed (Answer B is incorrect). Although bosentan is an attractive oral option to manage her PAH, her liver enzymes are elevated more than 3 times the upper limit of normal. Therefore, in this setting, administering bosentan is not recommended (Answer D is incorrect). If liver transaminases are elevated transiently because of hepatic congestion, bosentan can be reconsidered later. Because this patient is currently in functional class IV with advanced symptoms at rest, epoprostenol is indicated for a survival benefit (Answer C is correct).

#### **14. Answer: A**

Epoprostenol (Answer A is correct) is warranted to manage this patient's underlying disease because he has not responded to two oral PAH therapies; he is considered high risk because of his right ventricular dysfunction and low CI. He has normal filling pressures for a patient with right ventricular dysfunction, and diuresis with furosemide might only worsen his low CI (Answer

B is incorrect). The underlying cause of his low CI is not elevated arterial resistance; therefore, nitroprusside would probably worsen his hypotension (Answer C is incorrect). Correcting the elevated pulmonary pressures should correct the low CI; therefore, dobutamine is not indicated at this time because it would probably worsen his tachycardia (Answer D is incorrect).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: C**

In this patient, the presence of chest pain, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggests NSTE-ACS. Because of his presentation characteristics, he is at a high enough risk to warrant cardiac catheterization (invasive strategy). This invasive strategy is used to determine whether occluded or partly occluded epicardial arteries exist, which ones can be intervened on, and whether to perform PCI (percutaneous transluminal coronary angioplasty with or without stenting). Initial therapy for ACS usually consists of morphine, oxygen, nitroglycerin, and aspirin therapy, but only aspirin has been shown to reduce mortality from these initial treatments. Aspirin should be given as soon as possible after hospital presentation and continued indefinitely, if tolerated. According to clinical trials, guidelines, and experience, an initial dose of 162–325 mg is recommended (Answers B and D are not the best choices of dosing for an acute episode). Aspirin, together with a P2Y<sub>12</sub> receptor antagonist, is indicated for an early invasive strategy in the management of UA/NSTEMI, improving outcomes. The 2014 NSTE-ACS guidelines give a class I recommendation for clopidogrel, ticagrelor, and prasugrel in the ACS setting for patients undergoing PCI. The choice of which P2Y<sub>12</sub> receptor antagonist to use in the ACS setting depends on patient presentation, contraindications, and whether PCI is involved; in this case, any of the three P2Y<sub>12</sub> antagonists would be appropriate. The anticoagulation strategy treatment for ACS generally includes one anticoagulant (UFH, low-molecular-weight heparin, fondaparinux, or bivalirudin). When UFH is chosen as an anticoagulant strategy, the dose used for ACS is a 60-unit/kg bolus and a 12-unit/kg/hour infusion (Answer A is an incorrect dosing strategy). Regarding dosing, bivalirudin (Answer D) would be an appropriate anticoagulation strategy; however, the initial aspirin dose should be higher, and a nitroglycerin drip would not be the best choice, given his right-sided MI (low blood pressure, low heart rate). Intravenous β-blocker therapy (Answer A) is reasonable in patients without contraindications when hypertension or ongoing ischemia is a concern; however, initiating oral therapy within 24 hours is preferred in most patients as long as the patient has no signs of HF, evidence of low output state, increased

risk of cardiogenic shock, or other contraindications to β-blockade. β-Blockers should initially be avoided in this patient, given his blood pressure and heart rate. An intravenous ACE inhibitor (Answer B) should not be given to patients within the first 24 hours of ACS because of the increased risk of hypotension. Answer C includes DAPT and an appropriate dose of anticoagulant (Answer C is correct).

**2. Answer: A**

The NSTE-ACS guidelines recommend the use of one anticoagulant during an acute event. Enoxaparin, UFH, and bivalirudin are all recommended as class I agents for the invasive management of NSTE-ACS. However, fondaparinux (Answer C) is not optimal because increased risk of catheter-related thrombosis has been associated with fondaparinux use in the catheterization laboratory. The NSTE-ACS guidelines advise the use of additional heparin if fondaparinux was chosen as an initial anticoagulant when the patient underwent intervention, whereas the PCI guidelines give fondaparinux a class III or harmful recommendation. Of the remaining three options, UFH (Answer A) is preferred because of its rapid clearance. Both enoxaparin (Answer B) and bivalirudin (Answer D) are appropriate options but would need to be dose adjusted, given this patient's CrCl of less than 30 mL/minute/1.73 m<sup>2</sup>. Doses listed in Answers B and D would be appropriate for patients with a normal CrCl, however.

**3. Answer: B**

Given that this patient had a significantly low platelet count with his most recent heparin exposure and is believed to have HIT, using any of the GP IIb/IIIa inhibitors (Answers A and C) would be unwise for ACS treatment because these agents must be combined with UFH. Thrombolytic therapy (Answer D) is not recommended for treating NSTE-ACS and would be inappropriate in this patient. Bivalirudin (Answer B), a direct thrombin inhibitor, would be the treatment of choice in patients with HIT undergoing PCI.

**4. Answer: D**

Administration of β-blocker therapy carries a risk of causing HF decompensation, particularly when the β-blocker is titrated too quickly or initiated in

patients who are not euvolemic. Although administering  $\beta$ -blockers within the first 24 hours is beneficial in STEMI, this patient has several risk factors that would be considered contraindications to initial  $\beta$ -blockade. The clinical condition of this patient suggests he is not euvolemic, and aggressive diuresis should be attempted before initiating a  $\beta$ -blocker for him. In addition, intravenous  $\beta$ -blocker therapy (Answer B) would place him at an even greater risk of cardiogenic shock. Answers A and C are inappropriate because the doses are too aggressive for a patient with an EF of 25%. Answer D is correct; however, before discharge, this patient should be reevaluated for the initiation of low-dose  $\beta$ -blocker therapy.

#### 5. Answer: C

This patient is well perfused and can be classified in Forrester hemodynamic subset II (warm and wet). Because the patient has pulmonary congestion (shortness of breath, dyspnea at rest), intravenous diuretics are first-line therapy. Nitroglycerin (Answer C) is the best choice in this setting because vasodilatory agents can be used in conjunction with intravenous diuretics to improve acute pulmonary edema. When adjunctive therapy is needed in addition to loop diuretics, intravenous vasodilators should be considered over inotropic agents. Dobutamine (Answer A) and milrinone (Answer B) primarily increase CO, which is not a problem in warm and wet exacerbations. In addition, the adverse effects of these agents (increased mortality, proarrhythmia) limit their use. Intravenous metoprolol (Answer D) should be used extremely cautiously because of its negative inotropic effects and because this patient is not in a euvolemic state.

#### 6. Answer: D

This patient has a depressed LVEF less than 40%; therefore, her drug therapy options are limited. Procainamide (Answer A) is indicated only in secondary prevention of sustained VT in patients with a normal LVEF greater than 40%; if given to this patient, it could worsen her HF. Metoprolol (Answer B) is indicated for treating patients with asymptomatic nonsustained VT and SVT associated with CAD. This patient had an episode of sustained VT; therefore, therapy beyond  $\beta$ -blockade is warranted. Her QTc interval is not prolonged at 380 milliseconds, and her serum magnesium concentration is within normal limits, so she does not need intravenous

$\text{Mg}^{2+}$  therapy (Answer C). Amiodarone (Answer D) is a first-line treatment of patients without contraindications because of its efficacy and safety in patients with an LVEF less than 40%.

#### 7. Answer: B

This patient has target-organ damage from poorly controlled hypertension in the form of a cerebrovascular accident. Although fenoldopam (Answer A) is indicated for treating hypertensive emergencies, its use is cautioned in patients with stroke symptoms because its dopamine agonist activity can cause cerebral vasodilation and potentially reduced blood flow to the ischemic areas of the brain. Nicardipine (Answer B) is an appropriate choice for this patient because its calcium channel blocking effects will reduce blood pressure and potentially decrease vasospasm in the cerebral arteries, which can lead to further ischemia or seizure activity. Although labetalol (Answer C) is an effective option for treating this patient's hypertensive emergency, she has a history of asthma and a low heart rate, making labetalol a less-than-ideal option for treating her symptoms. The antihypertensive effects of enalaprilat (Answer D) depend on a patient's renin activity, which is unknown in this case. Therefore, the blood pressure-reducing effects may be more difficult to control than with a drug having a more consistent effect in individuals. In addition, the bolus nature of the drug is not ideal for tightly controlling blood pressure with no more than a 25% reduction in MAP. Continuous infusion drugs are preferable for easier titration to effect in a hypertensive emergency.

#### 8. Answer: C

This patient is experiencing hypertensive urgency, considering that he has no evidence of target-organ damage. Thus, his blood pressure may be reduced over 24 hours using oral medications. Given this patient's comitant comorbidities, HF, and microalbuminuria, an ACE inhibitor (Answer C) would be considered appropriate. Sublingual nifedipine (Answer A) is no longer recommended for management of hypertensive urgency because of acute blood pressure lowering and association with life-threatening adverse events, such as MI and stroke. Clonidine (Answer B) and labetalol (Answer D) are acceptable options; however, the patient has compelling indications for an ACE inhibitor. Although the patient should receive a  $\beta$ -blocker in addition to an

ACE inhibitor for HF management, labetalol is not one of the three  $\beta$ -blockers recommended for chronic HF management.

**9. Answer: C**

The Cardiac Arrest Study Hamburg trial compared ICD with AAD in survivors of cardiac arrest for secondary prevention of SCD. The propafenone (Answer A) study arm was discontinued early because of a significantly (61%) higher mortality rate than in the ICD arm (Answer A is incorrect). Although this trial had a small sample size that prevented a statistically significant difference in total mortality in ICD-treated patients versus patients treated with either amiodarone or metoprolol, the incidence of sudden death was significantly lower in patients with an ICD (Answer C is correct; 33% vs. 13%;  $p=0.005$ ). The Antiarrhythmics Versus Implantable Defibrillators trial also evaluated ICD implantation versus AAD therapy (primarily amiodarone) in survivors of SCD. Patients with ICDs had a significantly higher rate of survival than those treated with drug therapy (89% vs. 82%;  $p<0.02$ ), making Answer C preferable to all the other options (Answers B and D are incorrect).

**10. Answer: C**

The number needed to treat can be calculated as  $1/\text{Absolute risk reduction}$ . Because the absolute risk reduction in mortality at 60 months was 7.2% with ICD versus placebo,  $1/0.072$  would be used to calculate the number of patients needed to treat to prevent one death during this time. About 14 patients (Answer C) would need to be treated with ICD to prevent one death in 60 months versus placebo. Other calculations in this fashion, including relative risk reduction and  $100\% - \text{the absolute or relative risk reduction}$ , do not provide useful information for interpreting the trial results and yield an incorrect number of patients (Answers A, B, and D are incorrect).

**11. Answer: D**

International Pharmaceutical Abstracts (Answer A) is a database of primarily pharmaceutical abstracts in more than 750 journals, including foreign and state pharmacy journals, in addition to key U.S. medical and pharmacy journals. Many of the citations are not included on Medline, so a broader search can be performed; however, subject descriptors are not consistently defined in a uniform way, and multiword terms are often cited

backward. The Iowa Drug Information Service database (Answer B) offers full-text articles from 1966 to the present in about 200 medical and pharmacy journals (based primarily in the United States). It is updated monthly, and newly available articles may take longer to access from this service. The Clin-Alert database (Answer C) contains more than 100 medical and pharmacy journals focused on adverse events, drug interactions, and medical-legal issues. It is used primarily to look up adverse events (especially recent reports) associated with medications. Excerpta Medica (Answer D) is a comprehensive database of more than 7000 journals from 74 countries dating from 1974 to the present. Recently published articles appear in the system within 10 days of article publication, and it often contains data not found in a typical Medline search.

**12. Answer: B**

MedWatch is a post-FDA approval program established by the FDA for health care professionals to report the adverse events that occur after a drug is approved. Although it is commonly used only for reporting serious reactions to the FDA and would not be mandatory in this case (Answer A is incorrect), it can be used to report any adverse event. Information recorded on these forms is reported to the manufacturer and used to determine whether black box warnings are necessary or whether new adverse effects are seen with a drug. The Joint Commission requires that all institutions have a definition of an ADR for the institution that can be understood and remembered by all health care professionals (Answer B is correct). In addition, The Joint Commission requires that each drug dose administered be monitored for adverse effects, that each institution have a system in place for reporting ADRs, and that the institution ensure that the reporting mechanism identifies all key ADRs. The Naranjo algorithm is used to determine the likelihood of cause and effect from a presumed drug-induced event, but is not required (Answer C is incorrect). Answer D is incorrect as serious adverse effects are reportable to the FDA, as are severe and life-threatening events.

**13. Answer: B**

Because the pharmacy and therapeutics committee wants to discover whether the new drug is worth the extra cost for the added mortality benefits it can provide for patients with decompensated HF compared

with available therapies, a cost-effectiveness analysis (Answer B is correct) is the best pharmacoeconomic analysis to perform. Cost-minimization analysis (Answer A is incorrect) is used to determine whether a therapeutically equivalent drug within a class that provides the same therapeutic outcome as other available drugs can be used for less cost. Cost-utility analysis (Answer D is incorrect) is used to determine whether a drug can improve the quality of a patient's life more than other available therapies. Cost-benefit analysis (Answer C is incorrect) is used to evaluate new programs or services to determine whether they provide enough benefit to justify the cost of running the program.

